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

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Abstract

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*-fluoroalkenes 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(PPh₃)₄. The tertiary alkylzincs also produced desired fluoroalkenes in high yields. Coupling of 1,1-dichloroalkene with organozinc reagent resulted in the formation of mono-coupled product.

In the search for a more selective inhibitors of *S*-adenosyl-L-homocysteine (AdoHcy, **A**) hydrolase,¹ we attempted syntheses of AdoHcy analogues with 5',6'-olefin (or halovinyl) moieties incorporated in place of the sulfur atom (**B**; Figure 1).² Based on the known ability of the enzyme to add water across 5',6'-double bond,^{1c} we envisioned that such compounds should form "stable" complexes with the enzyme that would help to identify key binding groups at the active site of the enzyme that interact with the Hcy moiety and participate in subsequent elimination and hydrolytic activity steps.

Based on retrosynthetic analysis, we had previously attempted synthesis of analogues **B** (X = H) by (a) construction of a new C5'-C6' double bond *via* either Wittig or metathesis reactions or (b) formation of a new C6'-C7' single bond *via* Pd-catalyzed cross-couplings between readily available 6'-halo(or stannyl)homovinyl adenosine^{1a} derivatives (**C** or **D**) with the corresponding amino acid counterparts.² Since subsequent addition of bromine across C5'-C6' double bond in analogues of type **B** (X = H) followed by dehydrobromination (DBU) 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 group.³ However, despite the wide application of C_{sp}-C_{sp}² and C_{sp}²-C_{sp}² couplings, couplings involving C_{sp}³ centers are less explored⁴ with the exception of couplings between C_{sp}² as electrophiles and C_{sp}³ as nucleophiles.^{3c,4a} Moreover, the mono cross-coupling reactions of 1,1-dihalovinyl electrophiles with C_{sp}² or C_{sp}³ nucleophiles are less common⁵ and mono couplings between 1,1-dihalovinyl electrophiles and C_{sp}³ nucleophiles are scarce.^{3c,6} Panek *et al.* utilized a double coupling strategy with (α-iodo)vinyl silanes for the synthesis of trisubstituted alkenes in order to overcome difficulties in selective alkylation of vinyl dibromides.⁷ McCarthy^{8a} and Burton^{8b} and their coworkers developed coupling between 1-

bromo(or chloro)-1-fluoroalkenes with vinyl/aryl organostannanes and boranes in order 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 dihalohomovinyl 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-dihaloalkenes.^{3c,6} 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^{3c} coupling with alkylzincs. We expected formation of monoalkylated fluoroalkenes in view of inertness of fluorides^{3a} towards couplings. The terminal dihaloalkenes **4–6** were prepared in high yields by the McCarthy's procedure¹¹ which involves: (i) condensation of aldehydes **1a–c** and ketone **1d** with sulfonyl-stabilized 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^{1a} with NIS, NBS or Cl₂ to give 1-fluoro-1-iodo- (**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 dihalohomovinyl nucleoside or ribofuranosyl precursors of type **E** which also has an oxygen atom at 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 (³J_{F-H(trans)} = 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-Prelog priority at the reaction center carbon. The 1-fluorovinyl bromide **5a** and chloride **6a** also underwent efficient couplings with BrZn(CH₂)₃CO₂Et to give **7a(Z)** in 70% and 80% yield (entries 3 and 4). The calculated yields based only on the conversion of *E* isomers of **5a** and **6a** (from *E/Z*, 93:7 mixtures) to **7a(Z)** are 75% and 86%, respectively. Analogous treatment of **4a** (*E/Z*, 95:5) with alkylzinc bromides containing double bond [BrZn(CH₂)₃CH=CH₂] or acetal functionality [BrZn(CH₂)₂CH(OCH₂)₂] gave **8a(Z)** or **9a(Z)**, respectively (entries 5 and 6).

In order to optimize reaction conditions, we tested efficiency of various Pd catalysts for such Negishi monoalkylation (Scheme 3). We found that tris(dibenzylideneacetone)palladium [Pd₂(dba)₃] and 1,4-bis(diphenylphosphinobutane)palladium chloride [PdCl₂(dppb)] 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(dppf) were also less effective. Coupling of **4a** with BrZn(CH₂)₃CO₂Et in the presence of PdCl₂(dppb) 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(dppb) as catalyst (entry 12). The vinyl iodide **4c** (*E/Z*, 75:25) with benzyloxymethyl 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 fluoroalkene **8c(Z)** in moderate yield (56%, entry 17) in addition to unchanged **4c** with enriched *Z* to *E* ratio (56:44). The PdCl₂(dppb) catalyst not only increased the yield but also led to the formation of **8c** as mixture of *E/Z* isomers

(20:80, 86%; entry 18). Also bromide **5c** yielded **8c** as *E/Z* mixture in high yield (entry 19). The 1-fluorovinyl iodide **4d** derived from acetophenone served as convenient starting material for the synthesis of multisubstituted alkenes¹² **7d**(*Z*), **8d**(*Z*), and **9d**(*Z*) (entries 20–23).

In order to learn more about the stereochemical outcome of the couplings, pure *E* isomer and mixture enriched in *Z* isomer (*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 iododestannylation. Treatment of **4b**(*E*) with BrZn(CH₂)₃CO₂Et or BrZn(CH₂)₂CH(OCH₂)₂ [Pd(PPh₃)₄/12 h/65 °C] resulted in smooth conversion (GC/MS, ¹⁹F NMR) to **7b**(*Z*) or **9b**(*Z*) with isolated yields of 88% and 89%, 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, ¹⁹F NMR).

Generally, only in a few instances we observed formation (above detection limit¹³ of 1–2%, ¹⁹F NMR) of the corresponding *E* isomers *via cis*-couplings (entries 18, 19, 21). For example alkylation of **4c** (iodide) and **5c** (bromide) in the presence of PdCl₂(dppb) produced **8c** as *E/Z* (20:80) mixture. These results are in agreement with *trans*-selective mono cross-coupling of 1,1-dihaloalkenes reported previously.^{3c,5,6,14} Burton and coworkers 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 hinderence of vicinal *cis*-substituent.^{14a} They applied this finding for the kinetic resolution of the *E* and *Z* coupling products.^{8b,14}

The major by-product isolated from the coupling reactions resulted from the reductive homocoupling of dihalide components. For example, the selfcoupling product of **4a**, e.g. (*Z,Z*)-2,3-difluoro-1,4-diphenyl-1,3-butadiene **12**, was isolated in 8% yield (16% consumption of **4a**) from the reaction of **4a** with BrZn(CH₂)₃CH=CH₂ (entry 5) as well as from reactions of **4a** with branched alkylzincs.

We also examined the Pd-catalyzed coupling of 1,1-dihaloalkenes with branched alkylzincs. Thus, PdCl₂(dppb) was found to be effective for monoalkylation of **4a** (*E/Z*, 95:5) with *tert*-BuZnBr (**10a**) to provide **11a** (80%; 3 h, 50 °C; Scheme 4). The Pd₂(dba)₃ and Pd(PPh₃)₄ catalysts were less effective leading to the formation of a significant amount of selfcoupling by-product **12** [e.g., 20%, 40% consumption of **4a** for Pd(PPh₃)₄]. Interestingly, attempted couplings of **4a** with secondary 2- or 3-pentylzinc bromides (**10b** or **10c**) gave various amount of desired products **11b** or **11c** (in the range of 5–50%) along with the isomerization byproduct **11d** (35–70%) and selfcoupled 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 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.^{4a,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 β,β -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 monocoupled/reduced byproduct **18** (22%; Scheme 5). Analogous couplings in the presence of PdCl₂(dppb) produced **15** (53%) and **18** (15%) in addition to dialkylated product **17** (27%). Similar couplings with more reactive β,β -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, or bromo, or chloro)alkenes with alkylzincs, thus providing stereoselective access to the internal fluoroalkenes. The primary alkylzincs gave the best results but the tertiary alkylzincs also produced desired fluoroalkenes in high yields. The β,β -dichlorostyrene gave selective coupling to produce multisubstituted chloroalkenes. Application of 1,1-dihaloalkenes for selective double alkylation strategy which can be used for the synthesis of tetrasubstituted alkenes as well as synthesis of carbohydrate and nucleoside analogues of type **B** will be published elsewhere.

Experimental Section

Experimental procedures [Procedure A (synthesis of vinyl sulfones **2** *via* Wittig reaction), Procedure B (preparation of vinylstannane **3** *via* stannylsulfonate **2**), Procedure C (synthesis of dihaloalkenes **4–6** *via* halodestannylation of **3**), Procedure D (couplings of 1-fluoro-1-haloalkenes **4–6** with alkylzincs) and Procedure 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)-hexenoate (**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** (*E/Z*, 95:5; 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) to give **7a(Z)** (33 mg, 70%; 74% based on the conversion of *E* isomer only): ¹H NMR δ 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* = 39.4 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 δ 14.6, 22.1, 32.7 (d, ²*J*_{C-F} = 26.9 Hz), 33.6, 60.8, 106.9 (d, ²*J*_{C-F} = 8.5 Hz), 127.2, 128.7, 128.9, 134.0, 160.2 (d, ¹*J*_{C-F} = 266.7 Hz), 173.5; ¹⁹F NMR δ -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.

3,3-Dimethyl-2-fluoro-1-phenyl-1-butene (**11a**)

Treatment of **4a** (*E/Z*, 95:5, 40 mg, 0.16 mmol) with PdCl₂(dppb) (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 ¹⁹F NMR): ¹H NMR δ 1.15 (s, 9H), 5.40 (d, *J* = 40.7 Hz, 1H), 7.17–7.41 (m, 5H); ¹⁹F NMR δ -109.47 (d, *J* = 40.7 Hz); GC-MS *m/z* 178 [80%, M⁺; *t*_R = 10.78 min]. HRMS Calcd. for C₁₂H₁₅F (M+H⁺) 179.1237; Found: 179.1246.

(Z)-Ethyl 5-Chloro-6-phenyl-5-hexenoate (**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(dppf) (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%). Compound **15** had: ¹H NMR δ 1.19 (t, *J* = 7.1 Hz, 3H), 1.94 (quint, *J* = 7.1 Hz, 2H), 2.30 (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), 7.28–7.52 (m, 5H); ¹³C NMR δ 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⁺ [³⁵Cl]; *t*_R = 20.00 min). HRMS Calcd for C₁₄H₁₇35ClO₂ (M+H⁺): 253.0995; Found: 253.0989.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

- (a) Wnuk SF, Yuan CS, Borchardt RT, Balzarini J, De Clercq E, Robins MJ. *J Med Chem* 1994;37:3579–3587. [PubMed: 7932585] Yuan, C-S.; Liu, S.; Wnuk, SF.; Robins, MJ.; Borchardt, RT. *Advances in Antiviral Drug Design*. De Clercq, E., editor. 2. JAI Press; Greenwich: 1996. p. 41-88. (c) Wnuk SF. *Mini-Rev Med Chem* 2001;1:307–316. [PubMed: 12369977]
- Wnuk, SF.; Lalama, J.; Andrei, D.; Garmendia, C.; Robert, J. *S-Adenosylhomocysteine and S-ribosylhomocysteine analogues with sulfur atom replaced by the vinyl unit*. Abstracts of Papers, Carbohydrate Division, 229th National Meeting of the American Chemical Society; San Diego, CA. March 13–17, 2005; CARB-035 Jennifer, Lalama. MSc Thesis. Florida International University; 2004.
- de Meijere, A.; Diederich, F., editors. *Metal-Catalyzed Cross-Coupling Reactions*. Wiley-VCH; Weinheim: 2004. Miyaura, N., editor. *Top Curr Chem*. 219. 2002. (c) Negishi EI, Hu Q, Huang Z, Qian M, Wang G. *Aldrichimica Acta* 2005;38:71–88.
- For $C_{sp}C_{sp^2}$ (electrophile) $C_{sp}C_{sp^3}$ coupling see: (a) Negishi EI, Liu F, Diederich F, Stang P J *Metal-Catalyzed Cross-Coupling Reactions* Wiley-VCH Weinheim 1998 Chapter 1. 147 Dai C, Fu GC. *J Am Chem Soc* 2001;123:2719–2724. [PubMed: 11456957] For $C_{sp}C_{sp^2}$ (nucleophile) $C_{sp}C_{sp^3}$ see: (b) Menzel K, Fu G C *J Am Chem Soc* 2003;125:13642–13643. [PubMed: 14599185] For review on $C_{sp}C_{sp^3}$ $C_{sp^3}C_{sp^3}$ couplings see: (c) Cárdenas DJ. *Angew Chem Int Ed* 2003;42:384–387.
- (a) Roush WR, Moriarty KJ, Brown BB. *Tetrahedron Lett* 1990;31:6509–6512. (1,1-dibromoalkenes and vinylboronic acids). (b) Xu C, Negishi EI. *Tetrahedron Lett* 1999;40:431–434. Zeng X, Hu Q, Qian M, Negishi EI. *J Am Chem Soc* 2003;125:13636–13637. [PubMed: 14599182] Zeng X, Qian M, Hu Q, Negishi EI. *Angew Chem Int Ed* 2004;43:2259–2263. (1,1-dibromoalkenes and alkenyl zinc or zirconium). (c) Bryant-Friedrich A, Neidlein R. *Synthesis* 1995:1506–1510. Uenishi J, Matsui K. *Tetrahedron Lett* 2001;42:5353–5355. Shi JC, Zeng X, Negishi EI. *Org Lett* 2003;5:1825–1828. [PubMed: 12762662] Negishi EI, Shi JC, Zeng X. *Tetrahedron* 2005;61:9886–9895. [monoalkynylation of 1,1-dibromo(or chloro)alkenes]. (d) Shen W, Wang L. *J Org Chem* 1999;64:8873–8879. [PubMed: 11674792] (1,1-dibromoalkenes with aryl and vinylstannane). (e) Minato A. *J Org Chem* 1991;56:4052–4056. (1,1-chloroalkenes with arylzinc reagents)
- For the best of our knowledge the only successful Pd-catalyzed monoalkylation of vinyl dihalides was trans-selective monobutylation of 1,1-dichloro-2-phenylethene with $n-C_4H_9ZnCl$ in 81% yield (dibutylation product was obtained in 11%): (a) Minato A, Suzuki K, Tamao K. *J Am Chem Soc* 1987;109:1257–1258. Treatment of the (E/Z)-1-bromo-1-fluoroalkene with $BuLi/ZnCl_2/Pd(PPh_3)_4$ gave butylated Z-(fluoro)alkene and unchanged Z-isomer: (b) Lei X, Dutheil G, Pannecoucke X, Quirion JC. *Org Lett* 2004;6:2101–2104. [PubMed: 15200295] For iron(III)-catalyzed couplings see: (c) Santos MD, Franck X, Hocquemiller R, Figadere B, Peyrat JF, Provot O, Brion JD, Alami M. *Synlett* 2004:2697–2700.
- Arefolov A, Langille NF, Panek JS. *Org Lett* 2001;3:3281–3284. [PubMed: 11594814]
- (a) Chen C, Wilcoxon K, Huang CQ, Strack N, McCarthy JR. *J Fluorine Chem* 2000;101:285–290. (b) Xu J, Burton DJ. *Tetrahedron Lett* 2002;43:2877–2879.
- (a) Approaches in Ref. 8 required milder conditions than couplings of (α -fluoro)vinyl stannanes^{9b,c} and silanes^{9d} with alkenyl/aryl halides which needed addition of $CuI^{9b,c}$ and CsF^{9d} in order to overcome inductive electron-withdrawing effects of the α -fluorine atom that lower nucleophilicity of the stannanes and silanes.^{9e} On the other hand the same fluorine effect are expected to result in higher level of reactivity for α -fluorinated electrophilic components.⁸ (b) Chen C, Wilcoxon K, Zhu YF, Kim KI, McCarthy JR. *J Org Chem* 1999;64:3476–3482. [PubMed: 11674468] (c) Liu Q, Burton DJ. *Org Lett* 2002;4:1483–1485. [PubMed: 11975609] (d) Hanamoto T, Kobayashi T. *J Org Chem*

- 2003;68:6354–6359. [PubMed: 12895071] (e) Percy JM, Wilkes RD. Tetrahedron 1997;53:14749–14762. For the unexpectedly facile couplings of (α -fluoro)vinyl tris(trimethylsilyl)germanes see: (f) Wang Z, Gonzalez A, Wnuk SF. Tetrahedron Lett 2005;46:5313–5316.
10. (a) Only dialkylated and monoalkylated products have been isolated.² (b) Panek and coworkers reported⁷ that their attempts to selectively methylate vinyl dibromides under Negishi, Stille, or Suzuki conditions were unsuccessful despite the fact that differentiation of the two halogen groups for the C_{sp^2} – C_{sp^2} and C_{sp^2} – C_{sp^2} cross-couplings are known.⁵
11. McCarthy JR, Huber EW, Le TB, Laskovics M, Matthews DP. Tetrahedron 1996;52:45–58.
12. Itami K, Nokami T, Ishimura Y, Mitsudo K, Kamei T, Yoshida JI. J Am Chem Soc 2001;123:11577–11585. [PubMed: 11716711] (synthesis of tetrasubstituted alkenes via sequential couplings)
13. Robins MJ, Sarker S, Wnuk SF. Nucleosides Nucleotides 1998;17:785–790.
14. (a) Zhang X, Burton DJ. J Fluorine Chem 2001;47–54. (b) Xu J, Burton DJ. J Org Chem 2005;70:4346–4353. [PubMed: 15903310]
15. Hayashi T, Konishi M, Kobori Y, Kumada M, Higuchi T, Hirotsu K. J Am Chem Soc 1984;106:158–163.

FIGURE 1.
S-Adenosyl-L-homocysteine **A** and structure of the analogues **B** with sulfur atom replaced by “vinyl unit”

^a Key: (a) PhSO₂CHFPO(OEt)₂/LHMDS/THF/-78 °C; (b) Bu₃SnH/AIBN/benzene/Δ; (c) NIS/CH₂Cl₂; (d) NBS/CH₂Cl₂; (e) Cl₂/CH₂Cl₂.

Compds 1-6	R	R ¹
a	Ph	H
b	PhCH ₂ CH ₂	H
c	PhCH ₂ OCH ₂	H
d	Ph	CH ₃

Scheme 1.

Stereoselective synthesis of 1-fluoro-1-haloalkenes **4-6**^a

Scheme 2. Couplings of 1-fluoro-1-haloalkenes with alkylzincs^a^a Key: See Scheme 1 for description of R and R¹.

Scheme 3. Effect of the Pd catalysts on the efficiency of coupling^aKey: ^a 5% molar; ^b GC/MS and ¹⁹F NMR; ^c only Z product was detected; ^d 95% after 3.5 h; ^e Isolated yield 92%; ^f Isolated yield 94%.

Scheme 4. Couplings with branched alkylzincs Compounds **10**, **11**: Series **a** R = *tert*-Bu**b** R = 2-pentyl**c** R = 3-pentyl**d** R = *n*-pentyl

Scheme 5. Couplings with 1,1-dibromo- and 1,1-dichloroalkenes^a^a Key: (a) BrZn(CH₂)₃CO₂Et/PdCl₂(dppf)/THF/65 °C (oil-bath)

Table 1

Pd-catalyzed alkylation of 1-fluoro-1-haloalkenes **4-6**.^a

Entry	substrate	E/Z	product (Z)	time (h)	yield ^b	yield ^c
1	4a	95/5	7a	10	70%	74%
2	4a	95/5	7a^d	2	93%	97%
3	5a	93/7	7a	10	70%	75%
4	6a	93/7	7a	10	80%	86%
5	4a	95/5	8a^e	10	65%	69%
6	4a	95/5	9a^f	12	90%	94%
7	4a	95/5	9a^f	2	92%	96%
8	4a	95/5	9a^d	2	94%	98%
9	4b	78/22	7b	24	60%	78%
10	4b	100/0	7b	12	88%	88% ^g
11	4b	15/85	7b	24	14%	96%
12	4b	84/16	7b^d	8	82%	98%
13	4b	78/22	8b^h	20	66%	85%
14	4b	78/22	9b	20	74%	94%
15	4b	100/0	9b	12	89%	89% ⁱ
16	4b	15/85	9b	24	14%	96%
17	4c	75/25	8c	48	56% ^j	74%
18	4c	67/33	8c^{d,k}	4	86%	
19	5c	77/23	8c^{d,k}	6	84%	
20	4d	49/51	7d	24	45%	94%
21	4d	49/51	7d^{d,l}	8	60%	
22	4d	49/51	8d	24	45%	92%
23	4d	49/51	9d	24	46%	90%

^a Pd(Ph₃P)₄ was used as a catalyst unless otherwise specified (50–65 °C).

^b isolated yield.

^c isolated yield based on the conversion of the *E* isomer only.

^d PdCl₂(dppb) catalyst.

^e (Z,Z)-2,3-difluoro-1,4-diphenyl-1,3-butadiene **12** was also isolated (8%; 16% consumption of **4a**).

^f Pd₂(dba)₃ catalyst.

^g 96% based on GC-MS.

^h (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 (¹⁹F NMR).

ⁱ 98% based on GC-MS.

^j 56% based on ¹⁹F NMR.

^k (*E/Z*, 20:80).

l (E/Z, 16:84; based on ^{19}F NMR and GC-MS).