JOC*Note*

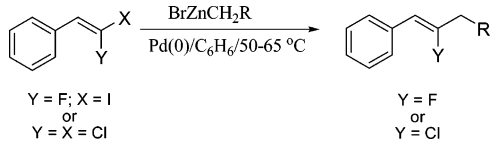
Synthesis of the Multisubstituted Halogenated Olefins via Cross-Coupling of Dihaloalkenes with Alkylzinc Bromides

Daniela Andrei and Stanislaw F. Wnuk*

Department of Chemistry and Biochemistry, Florida International University, Miami, Florida 33199

wnuk@fiu.edu

Received September 21, 2005



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 $Pd_2(dba)_3$ and $PdCl_2(dppb)$ catalysts but the best stereochemical outcome was obtained with less reactive $Pd(PPh_3)_4$. The tertiary alkylzincs also produced desired fluoroalkenes in high yields. Coupling of β,β-dichlorostyrene with organozinc reagent resulted in the formation of monocoupled product.

In the search for 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] On the basis of the known ability of the enzyme to add water across the 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.

On the basis of 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

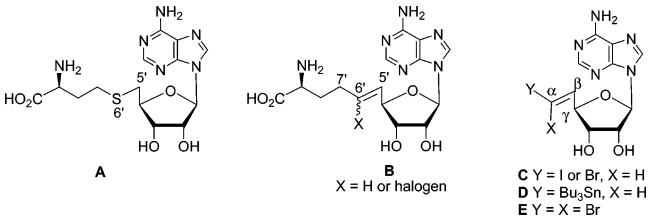


FIGURE 1. S-Adenosyl-L-homocysteine **A** and the structure of the analogues **B** with sulfur atom replaced by the "vinyl unit".

the corresponding amino acid counterparts.[2] Since subsequent addition of bromine across the C5′−C6′ double bond in analogues 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.[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 explored[4] 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} nucleophiles are less common[5] and monocouplings between 1,1-dihalovinyl electrophiles and C_{sp^3} nucleophiles are scarce.[3c,6] Panek et al. utilized a double coupling strategy with

(1) (a) Wnuk, S. F.; Yuan, C.-S.; Borchardt, R. T.; Balzarini, J.; De Clercq, E.; Robins, M. J. *J. Med. Chem.* **1994**, *37*, 3579−3587. (b) Yuan, C.-S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press: Greenwich, 1996; Vol. 2, pp 41−88. (c) Wnuk, S. F. *Mini-Rev. Med. Chem.* **2001**, *1*, 307−316.

(2) (a) Wnuk, S. F.; 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; American Chemical Society: Washington, DC, 2005; CARB-035. (b) Jennifer Lalama, M.Sc. Thesis, Florida International University, 2004.

(3) (a) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004. (b) *Topics in Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: New York, 2002; Vol. 219. (c) Negishi, E.-I.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichim. Acta* **2005**, *38*, 71−88.

(4) (a) For C_{sp^2}(electrophile)−C_{sp^3} coupling see: Negishi, E.-I.; Liu, F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 1, pp 1−47. Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719−2724. (b) For C_{sp^2}(nucleophile)−C_{sp^3} see: Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 3718−3719. (c) For C_{sp}(nucleophile)−C_{sp^3} see: Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642−13643. (d) For review on C_{sp^3}−C_{sp^3} couplings see: Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2003**, 42, 384−387.

(5) (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509−6512 (1,1-dibromoalkenes and vinylboronic acids). (b) Xu, C.; Negishi, E.-I. *Tetrahedron Lett.* **1999**, *40*, 431−434. Zeng, X.; Hu, Q.; Qian, M.; Negishi, E.-I. *J. Am. Chem. Soc.* **2003**, *125*, 13636−13637. Zeng, X.; Qian, M.; Hu, Q.; Negishi, E.-I. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259−2263 (1,1-dibromoalkenes and alkenyl zinc or zirconium). (c) Bryant-Friedrich, A.; Neidleim, R. *Synthesis* **1995**, 1506−1510. Uenishi, J.; Matsui, K. *Tetrahedron Lett.* **2001**, *42*, 5353−5355. Shi, J.-C.; Zeng, X.; Negishi, E.-I. *Org. Lett.* **2003**, *5*, 1825−1828. Negishi, E.-I.; Shi, J.-C.; 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 (1,1-dibromoalkenes with aryl- and vinylstannane). (e) Minato, A. *J. Org. Chem.* **1991**, *56*, 4052−4056 (1,1-chloroalkenes with arylzinc reagents).

(6) (a) To 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%): Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257−1258. (b) 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: Lei, X.; Dutheuil, G.; Pannecoucke, X.; Quirion, J.-C. *Org. Lett.* **2004**, *6*, 2101−2104. (c) For iron(III)-catalyzed couplings see: Santos, M. D.; Franck, X.; Hocquemiller, R.; Figadere, B.; Peyrat, J.-F.; Provot, O.; Brion, J.-D.; Alami, M. *Synlett* **2004**, 2697−2700.

10.1021/jo051980e CCC: $33.50
Published on Web 12/07/2005

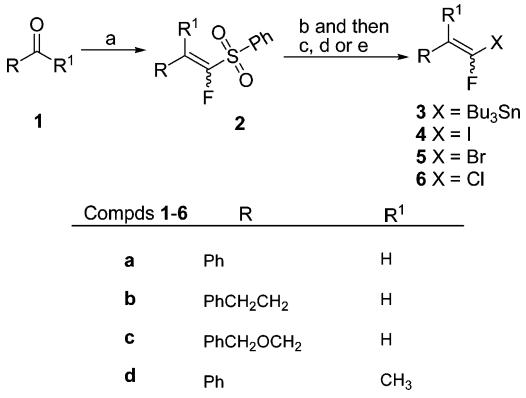
(α-iodo)vinyl silanes for the synthesis of trisubstituted alkenes to overcome difficulties in selective alkylation of vinyl dibromides.[7] McCarthy[8a] and Burton[8b] and their co-workers developed coupling between 1-bromo(or chloro)-1-fluoroalkenes with vinyl/aryl organostannanes and boranes to prepare 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 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 the inertia of fluorides[3a] toward couplings. The terminal dihaloalkenes **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 sulfonyl-stabilized fluorophosphonates to give (α-fluoro)vinyl sulfones **2**, (ii) radical stannyldesulfonylation with Bu_3SnH/AIBN to yield (α-fluoro)vinyl stannanes **3**, and (iii) the halodestannylation[1a] with NIS, NBS, or Cl_2 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 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 [$BrZn(CH_2)_3CO_2Et$] in the presence of $Pd(PPh_3)_4$ 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 $BrZn(CH_2)_3CO_2Et$ 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 [$BrZn(CH_2)_3CH{=}CH_2$] or acetal functionality [$BrZn(CH_2)_2CH(OCH_2)_2$] gave **8a**(*Z*) or **9a**(*Z*), respectively (entries 5 and 6).

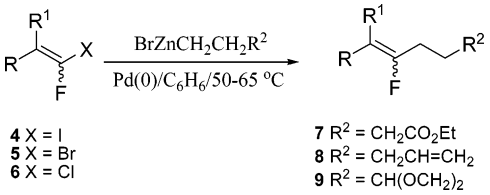
SCHEME 1. Stereoselective Synthesis of 1-fluoro-1-haloalkenes 4−6[a]



Compds **1-6**	R	R^1
a	Ph	H
b	$PhCH_2CH_2$	H
c	$PhCH_2OCH_2$	H
d	Ph	CH_3

[a] Reagents and conditions: (a) $PhSO_2CHFPO(OEt)_2$/LHMDS/THF/−78 °C; (b) Bu_3SnH/AIBN/benzene/Δ; (c) NIS/CH_2Cl_2; (d) NBS/CH_2Cl_2; (e) Cl_2/CH_2Cl_2.

SCHEME 2. Couplings of 1-Fluoro-1-haloalkenes with Alkylzincs[a]



[a] See Scheme 1 for description of R and R^1.

To optimalize reaction conditions, we tested efficiency of various Pd catalysts for such Negishi monoalkylation (Scheme 3). We found that tris(dibenzylideneacetone)palladium [$Pd_2(dba)_3$] and 1,4-bis(diphenylphosphinobutane)palladium chloride [$PdCl_2$(dppb)] gave smooth conversion of **4a** into **9a** in 2 h at 50 °C. The $Pd(PPh_3)_4$ effected only 11% conversion of **4a** into **9a** under analogous conditions and $Pd(OAc)_2$ and $PdCl_2$(dppf) were also less effective. Coupling of **4a** with $BrZn(CH_2)_3CO_2Et$ in the presence of $PdCl_2$(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 $Pd(PPh_3)_4$ 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 $PdCl_2$(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 $BrZn(CH_2)_3CH{=}CH_2$ [$Pd(PPh_3)_4$] 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 $PdCl_2$(dppb) catalyst not only increased the yield but also led to the formation of **8c** as a mixture of *E*/*Z* isomers

(7) Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2001**, *3*, 3281−3284.

(8) (a) Chen, C.; Wilcoxen, K.; Huang, C. Q.; Strack, N.; McCarthy, J. R. *J. Fluorine Chem.* **2000**, *101*, 285−290. (b) Xu, J.; Burton, D. J. *Tetrahedron Lett.* **2002**, *43*, 2877−2879.

(9) (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] 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 a higher level of reactivity for α-fluorinated electrophilic components.[8] (b) Chen, C.; Wilcoxen, K.; Zhu, Y.-F.; Kim, K.-I.; McCarthy, J. R. *J. Org. Chem.* **1999**, *64*, 3476−3482. (c) Liu, Q.; Burton, D. J. *Org. Lett.* **2002**, *4*, 1483−1485. (d) Hanamoto, T.; Kobayashi, T. *J. Org. Chem.* **2003**, *68*, 6354−6359. (e) Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1997**, *53*, 14749−14762. (f) For the unexpectedly facile couplings of (α-fluoro)-vinyl tris(trimethylsilyl)germanes see: Wang, Z.; Gonzalez, A.; Wnuk, S. F. *Tetrahedron Lett.* **2005**, *46*, 5313−5316.

(10) (a) Only dialkylated and monoalkylated products have been isolated.[2] (b) Panek and co-workers reported[7] 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 $C_{sp^2}-C_{sp}$ cross-couplings are known.[5]

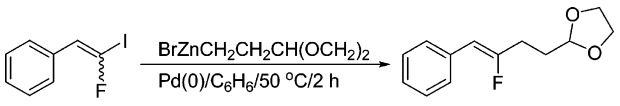
(11) McCarthy, J. R.; Huber, E. W.; Le, T.-B.; Laskovics, M.; Matthews, D. P. *Tetrahedron* **1996**, *52*, 45−58.

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**	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] $Pd(Ph_3P)_4$ 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] $PdCl_2$(dppb) catalyst. [e] (*Z*,*Z*)-2,3-Difluoro-1,4-diphenyl-1,3-butadiene **12** was also isolated (8%; 16% consumption of **4a**). [f] $Pd_2(dba)_3$ 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 (^{19}F NMR). [i] 98% based on GC-MS. [j] 56% based on ^{19}F NMR. [k] *E*/*Z*, 20:80. [l] *E*/*Z*, 16:84; based on ^{19}F NMR and GC-MS.

SCHEME 3. Effect of the Pd Catalysts on the Efficiency of Coupling[a]



4a (*E*/*Z*, 95:5) → **9a**(*Z*)

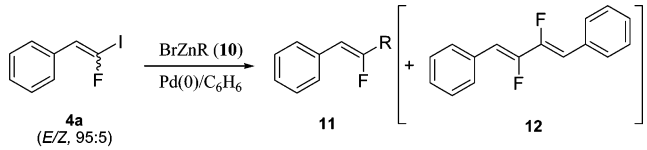
Catalyst[a]	Yield[b,c]
$Pd(PPh_3)_4$	11%
$PdCl_2$(dppf)	8%
$Pd(OAc)_2$	75%[d]
$Pd_2(dba)_3$	93%[e]
$PdCl_2$(dppb)	95%[f]

[a] 5% molar. [b] GC/MS and ^{19}F NMR. [c] Only *Z* product was detected. [d] 95% after 3.5 h. [e] Isolated yield 92%. [f] Isolated yield 94%.

(20:80, 86%; entry 18). Also bromide **5c** yielded **8c** as an *E*/*Z* mixture in high yield (entry 19). The 1-fluorovinyl iodide **4d** derived from acetophenone served as a convenient starting material for the synthesis of multisubstituted alkenes[12] **7d**(*Z*), **8d**(*Z*), and **9d**(*Z*) (entries 20−23).

To learn more about the stereochemical outcome of the couplings, pure *E* isomer and a mixture enriched in the *Z* isomer

SCHEME 4. Couplings with Branched Alkyzincs



Compounds **10, 11:** Series **a** R = *tert*-Bu
b R = 2-pentyl
c R = 3-pentyl
d R = *n*-pentyl

(*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 $BrZn(CH_2)_3CO_2Et$ or $BrZn(CH_2)_2CH(OCH_2)_2$ [$Pd(PPh_3)_4$/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 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, ^{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 $PdCl_2$(dppb) produced **8c** as an *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 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 isolated in 8% yield (16% consumption of **4a**) from the reaction of **4a** with $BrZn(CH_2)_3CH{=}CH_2$ (entry 5) as well as from reactions of **4a** with branched alkylzincs.

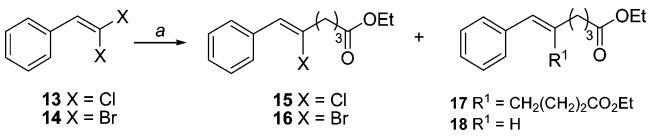
We also examined the Pd-catalyzed coupling of 1,1-dihaloalkenes with branched alkylzincs. Thus, $PdCl_2$(dppb) was found to be effective for monoalkylation of **4a** (*E*/*Z*, 95:5) with *t*-BuZnBr (**10a**) to provide **11a** (80%; 3 h, 50 °C; Scheme 4). The $Pd_2(dba)_3$ and $Pd(PPh_3)_4$ catalysts were less effective leading to the formation of a significant amount of self-coupling byproduct **12** [e.g, 20%, 40% consumption of **4a** for $Pd(PPh_3)_4$]. Interestingly, attempted couplings of **4a** with secondary 2- or 3-pentylzinc 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

(12) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2001**, *123*, 11577−11585 (synthesis of tetrasubstituted alkenes via sequential couplings).

(13) Robins, M. J.; Sarker, S.; Wnuk, S. F. *Nucleosides Nucleotides* **1998**, *17*, 785−790.

(14) (a) Zhang, X.; Burton, D. J. *J. Fluorine Chem.* **2001**, *112*, 47−54. (b) Xu, J.; Burton, D. J. *J. Org. Chem.* **2005**, *70*, 4346−4353.

SCHEME 5. Couplings with 1,1-Dibromo- and 1,1-Dichloroalkenes[a]



[a] Reagents and conditions: (a) $BrZn(CH_2)_3CO_2Et/PdCl_2(dppf)/THF/65$ °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.[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 [$PdCl_2$(dppf)/THF/65 °C/14 h] with $BrZn(CH_2)_3CO_2Et$ 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 $PdCl_2$(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 [A (synthesis of vinyl sulfones **2** via Wittig reaction), B (preparation of vinylstannane **3** via stannyldesulfonylation **2**), 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*)-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 $Pd(PPh_3)_4$ (7 mg, 0.006 mmol) under N_2. The resulting mixture was heated at 65 °C for 5 h. Additional $Pd(PPh_3)_4$ (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 ($NaHCO_3/H_2O$//EtOAc). The organic layer was washed (brine), dried (Na_2SO_4), evaporated, and chromatographed (hexane → 15% EtOAc/hexane) to give **7a**(*Z*) (33 mg, 70%; 74% based on the conversion of *E* isomer only): ^{1}H 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); ^{13}C NMR δ 14.6, 22.1, 32.7 (d, $^2J_{C-F}$ = 26.9 Hz), 33.6, 60.8, 106.9 (d, $^2J_{C-F}$ = 8.5 Hz), 127.2, 128.7, 128.9, 134.0, 160.2 (d, $^1J_{C-F}$ = 266.7 Hz), 173.5; ^{19}F NMR δ −102.20 (dt, J = 39.8, 19.7 Hz); MS *m*/*z* 237 (100%, MH^+). Anal. Calcd for $C_{14}H_{17}FO_2$ (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 $PdCl_2$(dppb) (6.0 mg, 0.01 mmol) gave **71**(*Z*) (93%).

3,3-Dimethyl-2-fluoro-1-phenyl-1-butene (11a). Treatment of **4a** (*E*/*Z*, 95:5, 40 mg, 0.16 mmol) with $PdCl_2$(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 ^{19}F NMR): ^{1}H NMR δ 1.15 (s, 9H), 5.40 (d, J = 40.7 Hz, 1H), 7.17−7.41 (m, 5H); ^{19}F NMR δ −109.47 (d, J = 40.7 Hz); GC-MS *m*/*z* 178 [80%, M^+; t_R = 10.78 min]. HRMS Calcd for $C_{12}H_{15}F$ ($M + H^+$) 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 $PdCl_2$(dppf) (24 mg, 0.029 mmol) under N_2. The resulting mixture was heated at 65 °C overnight. Volatiles were evaporated and the residue was partitioned ($NaHCO_3/H_2O$//EtOAc). The organic layer was washed (brine), dried (Na_2SO_4), evaporated, and chromatographed (hexane → 10% EtOAc/hexane) to give **15** (47 mg, 65%) and **18** (14 mg, 22%). **15**: ^{1}H 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); ^{13}C 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^+ [^{35}Cl]; t_R = 20.00 min). HRMS calcd for $C_{14}H_{17}{}^{35}ClO_2$ ($M + H^+$) 253.0995, found 253.0989.

Acknowledgment. This investigation was partially supported by NIH/NIGMS S06GM08205. The support of US ARO (W911NF-04-1-0022) for the purchase of the 600 MHz NMR spectrometer is acknowledged.

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

JO051980E

(15) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158−163.