JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

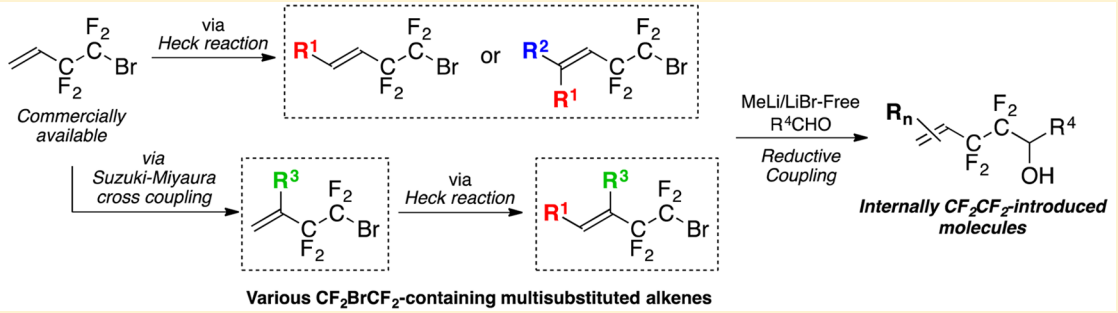
Stereochemically Defined Various Multisubstituted Alkenes Bearing a Tetrafluoroethylene ($-CF_2CF_2-$) Fragment

Yukiho Sakaguchi,[†] Shigeyuki Yamada,[†] Tsutomu Konno,*[,†] Tomohiro Agou,[‡] and Toshio Kubota[‡]

[†]Faculty of Molecular Chemistry and Engineering, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan

[‡]Department of Materials Science, Ibaraki University, 4-12-1 Nakanarusawa, Hitachi 316-8511, Japan

Supporting Information



ABSTRACT: Highly regio- and stereoselective transformation of commercially available 4-bromo-3,3,4,4-tetrafluoro-1-butene into multisubstituted alkenes having a tetrafluoroethylene fragment through Heck reactions and/or Suzuki–Miyaura cross-coupling reactions was established. Thus, the obtained alkenes underwent a smooth reductive coupling reaction with aldehydes under the influence of MeLi/LiBr-free, affording structurally unprecedented fluorinated materials.

INTRODUCTION

Significant interest has been expressed in organic molecules incorporating fluorine and/or fluorine-containing functional groups in the fields of materials, pharmaceutical, and medicinal chemistry, since a fluorine can very often bring about a drastic effect on the molecular characteristics owing to the unique nature of a fluorine atom.[1] There have been reported a large number of fluorine-containing organic molecules so far, but they have been still limited to the synthesis of molecules containing typical F, CF_3, and C_nF_{2n+1} ($n \geq 4$) groups. In order to expand an availability of organofluorine compounds, consequently, development of novel synthetic methods to effectively prepare unprecedented fluorinated compounds still remains a primary concern and an important subject in materials chemistry as well as medicinal chemistry.[2]

To fulfill such demands, our group has focused on the development of fluorinated substances with unprecedented frameworks and on the exploitation of their novel molecular properties.[3] Particularly, in recent years, we have devoted significant effort to developing convenient and efficient synthetic methods for the preparation of organic compounds with a perfluoroalkylene group:[4] e.g., a tetrafluoroethylene ($-CF_2CF_2-$) fragment.[5] This is because wholly new molecular features can be imparted to the parent molecules through the perfluoroalkylene fragment. In fact, Linclau et al. have reported that the polar and hydrophobic character of tetrafluorinated sugars, e.g. **1a**,**b**, leads to a drastic improvement in the contacts between a carbohydrate analogue and its host protein in a significant manner: that is, the hydrophobic desolvation effect caused by the tetrafluoroethylene fragment plays a favorable role in the molecular recognition processes (Figure 1).[6] Our research group has also successfully developed some organic molecules containing tetrafluoroethylene fragments (**2a**–**c**),

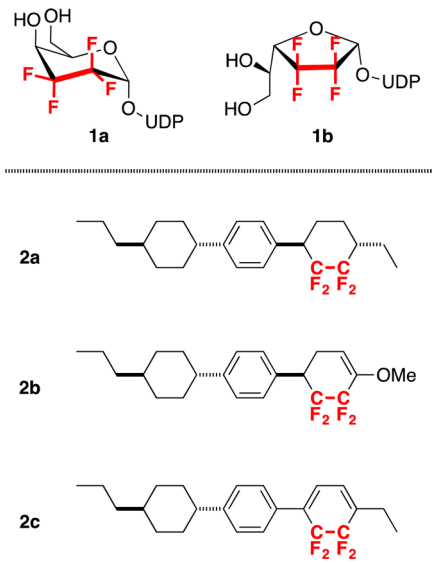
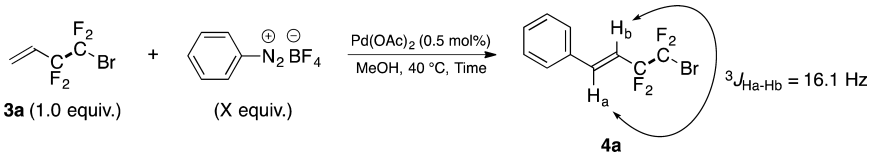


Figure 1. Application examples of tetrafluorinated materials.

Received: November 22, 2016
Published: January 10, 2017

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618–1631

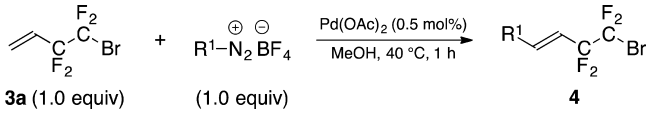
Table 1. Investigation of the Reaction Conditions for the Heck Reaction of 3a with Phenyldiazonium Salt

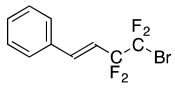
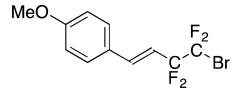
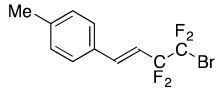
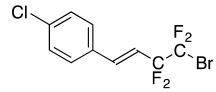
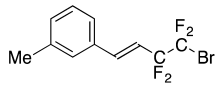
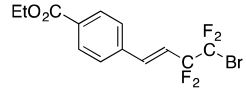
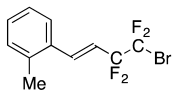
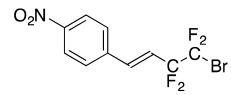


entry	X/equiv	time/h	yield of 4a[a]/%
1	1	0.25	64
2	1	1	84 (71)
3	1	2	82
4	2	1	79

[a]Determined by ^{19}F NMR. The value in parentheses is the isolated yield.

Table 2. Heck Reactions of 3a with Various Types of Aryldiazonium Tetrafluoroborates



Entry		Product	Yield[a]/%	Entry		Product	Yield[a]/%
1	**4a**		84 (71)	5	**4e**		6
2	**4b**		56 (54)	6	**4f**		quant. (88)
3	**4c**		48 (37)	7	**4g**		quant. (88)
4	**4d**		45 (36)	8	**4h**		quant. (87)

[a]Determined by ^{19}F NMR. Values in parentheses are the isolated yields.

and we have proved that such tricyclic molecules exhibit a large negative dielectric anisotropy by a significant enhancement of the molecular dipole in a minor axis induced from the $-CF_2CF_2-$ component, which is an unprecedented structural motif for promising negative-type liquid crystals employed in VA-mode LC display devices (Figure 1).[7]

Consequently, a tetrafluoroethylene fragment included in a molecular structure can often significantly enhance the potent properties or impart novel and intriguing molecular characteristics. Therefore, much attention has been paid to the development of novel synthetic methods for tetrafluoroethylenated organic molecules as well as the investigation of their molecular characteristics. However, the design and synthesis of such substances still remains an underdeveloped area, and further studies on the development of completely new synthetic methods for their preparation are highly desirable.[8]

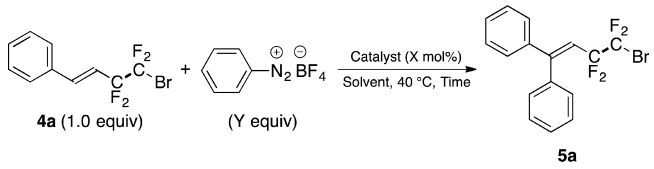
In this article are disclosed in detail novel synthetic methods for various multisubstituted alkenes with a tetrafluoroethylene fragment in a highly stereoselective manner from commercially available 4-bromo-3,3,4,4-tetrafluoro-1-butene.

RESULTS AND DISCUSSION

Highly Stereoselective Synthesis of 1,2-Disubstituted Alkenes via Heck Reaction of 4-Bromo-3,3,4,4-tetrafluoro-1-butene. Initially, we addressed a synthetic transformation of an alkene moiety in the commercially available 4-bromo-3,3,4,4-tetrafluoro-1-butene (**3a**) as an effective approach to various organofluorine compounds: we attempted a palladium-catalyzed Heck reaction[9] with phenyldiazonium tetrafluoroborate.[10,11] As shown in entry 1 (Table 1), on treatment of 1.0 equiv of **3a** with 1.0 equiv of the diazonium salt under the influence of 0.5 mol % of $Pd(OAc)_2$ in MeOH at

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631

Table 3. Investigation of the Reaction Conditions for the Second Heck Reaction of 4a with a Tetrafluoroethylene Fragment



entry	catalyst, *X*/mol %	*Y*/equiv	solvent	time/h	yield of **5a**[a]/%	recovery of **4a**[a]/%
1	$Pd(OAc)_2$, 5	1.2	MeOH	2	8	86
2	$Pd(PPh_3)_4$, 5	1.2	MeOH	2	2	96
3	$Pd_2(dba)_3$, 2.5	1.2	MeOH	2	4	96
4	$Pd_2(dba)_3{\cdot}CHCl_3$, 2.5	1.2	MeOH	2	4	96
5	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4PPh_3$, 2.5	1.2	MeOH	2	3	97
6	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + 2dppe, 2.5	1.2	MeOH	2	2	98
7	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 2.5	1.2	MeOH	2	19	81
8	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 2.5	1.2	THF	2	0	quant
9	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 2.5	1.2	1,4-dioxane	2	0	quant
10	$[Pd_2(dba)_3{\cdot}HCl_3]$ + $4P(o\text{-Tol})_3$, 2.5	1.2	EtOH	2	3	97
11	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 2.5	1.2	MeOH	24	25	73
12	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 2.5	1.2	MeOH	48	24	64
13	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 10	1.2	MeOH	24	40	59
14	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 10	3.3	MeOH	24	88 (73)	8
15	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 10	5.5	MeOH	24	94	6
16	$[Pd_2(dba)_3{\cdot}CHCl_3]$ + $4P(o\text{-Tol})_3$, 10	3.3	MeOH	168	91	8

[a]Determined by ^{19}F NMR. The value in parentheses is the isolated yield.

40 °C for 15 min, the desired Heck product **4a** was obtained in 64% yield. Prolonged reaction time brought about a significant improvement in the chemical yield, the **4a** being obtained in 84% yield (entry 2). Further prolonged reaction time, however, did not result in further enhancement in the yield (entry 3). Additionally, increasing the amount of the diazonium salt caused a slight decrease in the yield (entry 4). In all cases, the product **4a** was solely obtained without forming any regio- and stereoisomers as side products. A careful ^1H NMR analysis of **4a** revealed that the coupling constant between H_a and H_b was 16.1 Hz, strongly indicating that the stereochemistry of the **4a** at the olefinic moiety was *E*.

Having the optimum reaction conditions for the Heck reaction in hand, we next performed the Heck reaction with various types of aryldiazonium salts. The results are summarized in Table 2.

Introduction of an electron-donating group, such as a methyl group, on the benzene ring of aryldiazonium salts significantly retarded the coupling reaction, resulting in the formation of products **4b−d** in 45−56% yields. It was proved, however, that the Heck reaction of **3b** occurred without a large influence on the position of the substituent on the benzene ring of aryldiazonium salt (entries 2−4). In addition, the use of a more strongly electron donating group, such as a methoxy group, led to only 6% formation of the corresponding adduct (entry 5). In stark contrast, electron-withdrawing substituents, such as chloro, ethoxycarbonyl, and nitro groups, on the benzene ring of aryldiazonium salts drastically promoted the Heck reaction, providing the corresponding adducts **4f−h** in a quantitative yield (entries 6−8). In all cases, *E*-configured Heck products were exclusively obtained,[12] and no *Z* isomers were detected at all.

Stereoselective Synthesis of Trisubstituted Alkenes via the Second Heck Reaction of the Heck Products 4. In order to extend our stereoselective Heck reaction to a novel and effective synthetic protocol for the preparation of trisubstituted alkenes with a tetrafluoroethylene fragment, our next effort was directed toward the second Heck reaction of the Heck product **4** obtained above. The results are collected in Table 3.

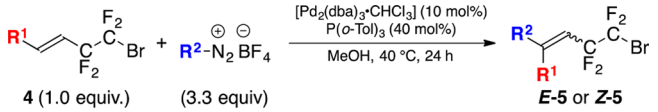
We first attempted Heck reaction of **4a** with phenyldiazonium tetrafluoroborate under almost the same reaction conditions as employed in Table 2. Thus, treatment of 1.0 equiv of **4a** with 1.2 equiv of phenyldiazonium tetrafluoroborate in the presence of 5 mol % of $Pd(OAc)_2$ in MeOH at 40 °C for 2 h led to a slight formation of the corresponding Heck product **5a**, together with a large recovery of the starting **4a** (entry 1). In order to exploit the optimum reaction conditions for the second Heck reaction, various palladium catalysts, as shown in entries 2−7, were thoroughly tested, and it was revealed that a bulky $P(o\text{-Tol})_3$-coordinated palladium catalyst was found to be the catalyst of choice, leading to a slight increase in the yield of **5a** (entry 7). Switching the solvent from MeOH to THF, 1,4-dioxane, and EtOH gave no satisfactory results (entries 8−10). Prolonged reaction time and increased catalyst loading was found to be slightly effective for the second Heck reaction, resulting in a beneficial improvement in the yield (entries 11−13). Finally, the use of over 3.3 equiv of the diazonium salt led to satisfactory results, affording the desired trisubstituted alkene **5a** in up to 94% yield (entries 14−16).

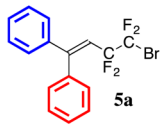
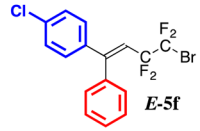
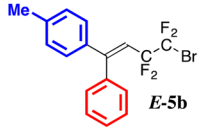
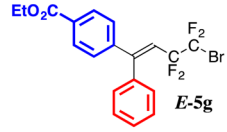
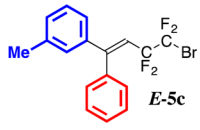
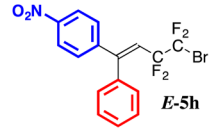
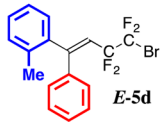
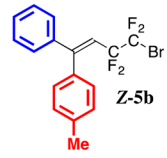
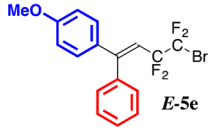
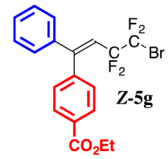
With the established viable reaction conditions (Table 3, entry 14), the second Heck reaction was demonstrated to obtain the trisubstituted alkenes using a variety of the first Heck products **4** and aryldiazonium salts. The results are shown in Table 4.

As shown in entries 2 and 3 of Table 4, the position of the substituent on the benzene ring of the diazonium salt significantly affected the reaction. Thus, meta and para substitution on the benzene ring of the diazonium salts led to moderate to high yields (entries 2 and 3), while ortho substitution resulted in poor yield (entry 4). In addition, *p*-

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631

Table 4. Heck Reactions of 4 with Various Types of Aryldiazonium Tetrafluoroborates



Entry	Major Product	Yield[a]/ % [E:Z][b]	Recovery[a] /% of 4	Entry	Major Product	Yield[a]/ % [E:Z][b]	Recovery[a] /% of 4
1	 5a	88 (73) [-]	8	6	 E-5f	85 (78) [96:4]	1
2	 E-5b	85 (75) [80:20]	13	7	 E-5g	86 (76) [99:1]	1
3	 E-5c	40 (34) [83:17]	59	8	 E-5h	78 (67) [99:1]	3
4	 E-5d	6 [N.D.[c]]	93	9	 Z-5b	91 (90) [26:74]	3
5	 E-5e	36 (23) [86:14]	61	10	 Z-5g	72 [3:97]	26

[a]Determined by ^{19}F NMR. Values in parentheses are isolated yields. [b]Values in brackets are the ratios of *E* and *Z* isomers, which were determined by ^{19}F NMR. [c]Not determined.

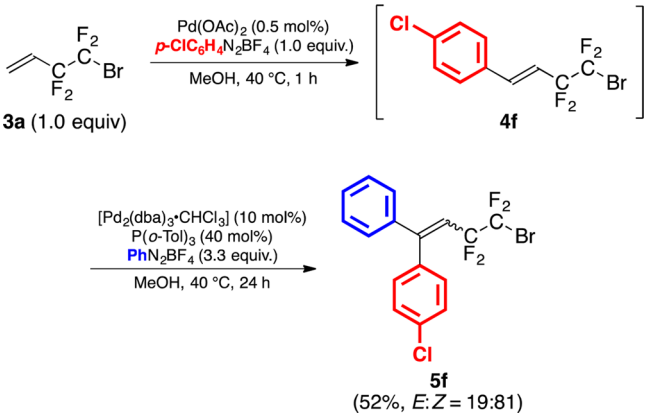
anisyldiazonium tetrafluoroborate also caused an unsatisfactory result (entry 5). In contrast, as shown in entries 6−8, the second Heck reaction of **4** with aryldiazonium salts having an electron-withdrawing group, such as chloro, ethoxycarbonyl, and nitro substituents, on the benzene ring, proceeded very smoothly to give the corresponding Heck adduct **5** in high yields as well as in a highly stereoselective manner. From these results, we found that the second Heck reaction was drastically influenced by the electron density of the aryldiazonium salt: the use of electron-abundant aryldiazonium salts did not give a complete consumption of the starting **4**, though the electron-deficient aryldiazonium salt led to full conversion of **4**. In addition, the electron density of the aryldiazonium salt also affected the stereoselectivity of the Heck product: approximately *E*:*Z* = 80:20 in the case of **5b−e** coupled with electron-abundant aryldiazonium salts, whereas almost exclusive *E* selectivity was observed in **5f−h** using electron-deficient aryldiazonium salts.

The reaction of **4b** having a tolyl group with the phenyldiazonium salt took place smoothly to afford the corresponding product **5b** in an excellent yield but in a relatively lower stereoselective manner (entry 9). Switching the substituent on the benzene ring in **4** from an electron-donating methyl group to an electron-withdrawing ethoxycarbonyl group caused suppression of the reaction, affording the desired product **5g** in 72% yield together with 26% recovery of the starting **4g**, while the isomeric ratio of the product **5g** was very high (entry 10).

To realize development of an environmentally benign synthetic protocol for multisubstituted alkenes bearing tetrafluoroethylene fragments, we attempted successive Heck reactions in one pot without isolation of the first Heck product **4** (Scheme 1). Thus, treatment of the starting **3a** with aryldiazonium tetrafluoroborate with a chlorine atom in the presence of palladium catalyst in MeOH at 40 °C for 1 h, followed by the successive addition of phenyldiaznoium salt and a suitable palladium catalyst under the optimum reaction

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631

Scheme 1. One-Pot Synthesis of Trisubstituted Alkenes Bearing a Tetrafluoroethylene Fragment



conditions, successfully afforded the corresponding trisubstituted alkene **5f** in an acceptable yield in two steps, though with a slight decrease in the stereoselectivity.

The stereochemistry of the major isomer of **5f** in entry 6 of Table 4 was unambiguously determined as *E*, on the basis of the result from X-ray crystallographic analysis of ***E*-5f**, as shown in Figure 2. The stereochemical determination of the other products was made on the basis of the reaction mechanism, as described in the next section, in addition to the X-ray crystallographic analysis of ***E*-5f**.

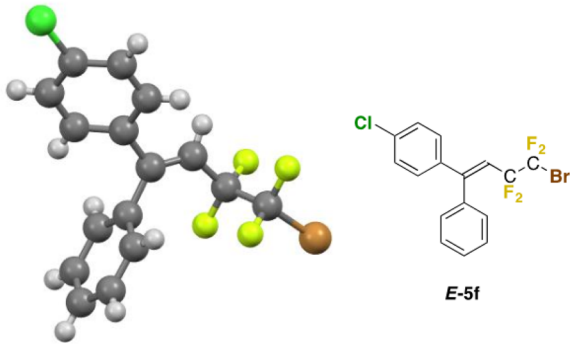


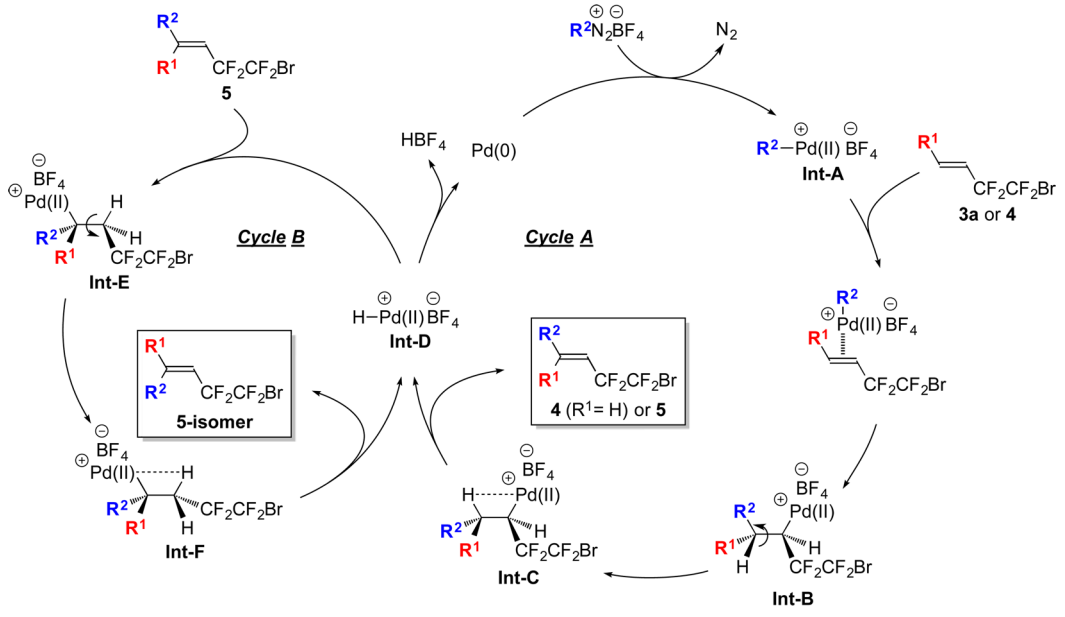
Figure 2. X-ray crystallographic analysis of ***E*-5f**.

Reaction Mechanism. The above results allow us to draw the reaction mechanism as shown in Scheme 2. Thus, oxidative addition of an aryldiazonium salt to Pd(0)[13] leads to the corresponding arylpalladium complex **Int-A**. Then coordination of **3a** (R^1 = H in cycle A) to the palladium metal center of **Int-A** and subsequent insertion into the R^2–Pd bond provides the palladium complex **Int-B**. Carbon–carbon bond rotation in **Int-B** can easily proceed to form **Int-C**, which undergoes *β* elimination to afford the Heck product **4** and **Int-D**. Finally, reductive elimination of **Int-D** regenerates Pd(0), together with HBF_4.

The second Heck reaction (R^1 = aryl in cycle A) also proceeds in the same manner as the first Heck reaction to produce the second Heck adduct **5** and **Int-D**. As a reason for the slight decrease of the stereoselectivity of **5**, we suggest that another catalytic cycle (cycle B) may exist to form an opposite stereoisomer. Thus, it is highly possible that **Int-D** may partially coordinate with the formed **5**, followed by insertion into the H–Pd bond, affording the corresponding palladium complex **Int-E** in cycle B.[14] Subsequently, **Int-E** can be easily converted into **Int-F** through carbon–carbon bond rotation, followed by immediate *β* elimination, giving rise to the opposite stereoisomer **5-isomer**.[15,16] When either R^1 or R^2 is an electron-deficient aromatic substituent with an electron-withdrawing group, the electron density at the double bond of **5** may be somewhat decreased, which retards the coordination of **5** to **Int-D**. Accordingly, the isomerization process does not occur very often, resulting in high stereoselectivity when the Heck product **5** contains an electron-deficient aromatic ring, whereas a slight decrease in stereoselectivity was observed when obtaining **5** with an electron-donating substituent on the aromatic ring.

Convenient Synthesis of 1,1-Disubstituted Alkenes with a Tetrafluoroethylene Fragment. At this point, we attempted to synthesize a different type of tetrafluoroethylenated alkene: namely, a 1,1-disubstitituted alkene with both an

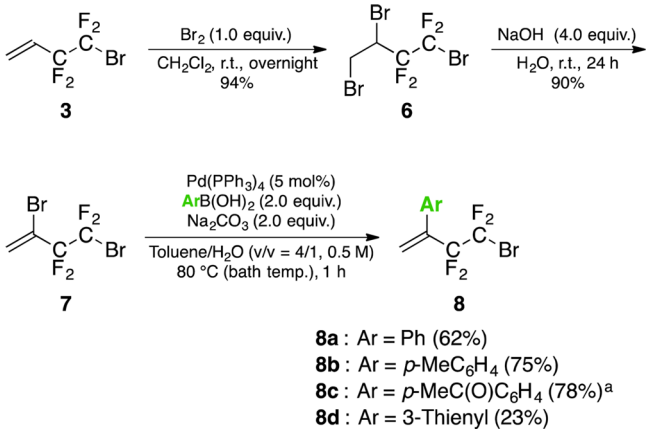
Scheme 2. Plausible Reaction Mechanism



DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618–1631

aryl substituent and a tetrafluoroethylene fragment at the same carbon. The 1,1-disubstituted alkenes **8** could be easily synthesized via a Suzuki–Miyaura cross-coupling reaction as a key reaction, as shown in Scheme 3.

Scheme 3. Synthesis of Various 1,1-Disubstituted Alkenes Bearing a Tetrafluoroethylene Fragment



[a]The cross-coupling reaction was carried out for 8 h.

Thus, treatment of 1.0 equiv of **3a** with 1.0 equiv of Br_2 in CH_2Cl_2 at room temperature overnight gave the dibrominated adduct **6** in 94% yield.[17] Then, **6** was subjected to NaOH aqueous solution (4.0 equiv) at room temperature for 1 day, affording the HBr-elimination product **7** in 90% yield.[18] A subsequent Suzuki–Miyaura cross-coupling reaction of **7** with various arylboronic acids, such as phenyl-, *p*-methoxyphenyl-, and *p*-acetylphenylboronic acids, proceeded smoothly to give the desired 1,1-disubstituted alkenes with a tetrafluoroethylene fragment, **8a–c**, in high yields.[19] In contrast, the cross-coupling reaction of **7** with 3-thienylboronic acid proceeded sluggishly to afford the adduct **8d** in poor yield.

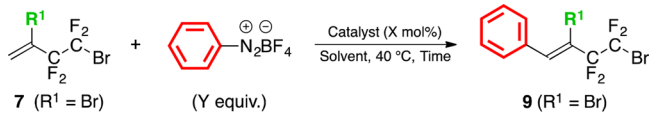
Stereoselective Synthesis of Various Trisubstituted Alkenes via the Heck Reaction of 7 or 8. In order to further synthesize different types of trisubstituted alkenes with a tetrafluoroethylene fragment, we demonstrated the Heck reaction of **7** and **8** with aryldiazonium salts. The results of investigating the reaction conditions are summarized in Table 5.

Thus, treatment of 1.0 equiv of **7** with 1.0 equiv of phenyldiazonium tetrafluoroborate in the presence of 0.5 mol % of $Pd(OAc)_2$ in MeOH at 40 °C for 1 h resulted in a complete recovery of the starting material (Table 5, entry 1). However, no change was observed even though the catalyst loading was increased up to 10 mol % (entry 2). Additionally, alteration of the palladium catalyst from $Pd(OAc)_2$ to phosphine-ligated palladium catalysts also did not lead to satisfactory results (entries 3 and 4). Use of EtOH or DMF as a solvent, instead of MeOH, did not afford the desired product **9** at all (entries 5 and 6).

In sharp contrast, substitution of R^1 from Br to Ph contributed to an incredible enhancement in the yield of Heck product, **10a** being obtained in 91% yield with an isomeric ratio of *E*:*Z* = 96:4 (Table 5, entry 7). At this time, a small amount of the starting **8a** (9%) still remained unreacted. A prolonged reaction time slightly improved the yield, but a small amount of the starting material was still recovered (entries 8 and 9). Increasing the amount of the diazonium salt by 20% led to complete consumption of **8a**, providing the desired Heck adduct **10a** in 95% yield in a highly stereoselective manner (entry 10), whereas a decrease in the catalyst loading from 10 to 5 mol % led to a significant drop in the yield (entry 11). The stereochemistry of the major isomer of **10a** was obviously determined as *E* by X-ray crystallographic analysis, as shown in Figure 3.

With the optimized reaction conditions in hand, we surveyed the substrate scope of this Heck reaction (Table 6). The position of the substituent on the benzene ring in aryldiazonium salts somewhat affected the yield of the Heck product **10**. Thus, aryldiazonium salts having a methyl substituent at the para- or meta position of the benzene ring gave the Heck adducts **10b,1c** in high yields in a highly stereoselective manner (entries 2 and 3). On the other hand, a slight decrease in the stereoselectivity was observed in the case of an ortho-substituted aryldiazonium salt, though the chemical

Table 5. Investigation of the Reaction Conditions for the Heck Reaction with 7 or 8a



entry		catalyst ((*X*/mol %)	*Y*/equiv	solvent	time/h		yield of **9** or **10a**[a]/%	*E*:*Z*[a]	recovery of **7** or **8a**[a]/%
1	**7**	$Pd(OAc)_2$ (0.5)	1.0	MeOH	1	**9**	0		quant
2		$Pd(OAc)_2$ (10)	1.0	MeOH	1		0		quant
3		$Pd(OAc)_2$ + 2P(*o*-Tol)$_3$)	1.0	MeOH	1		0		98
4		$Pd(PPh_3)_4$ (10)	1.0	MeOH	1		0		89
5		$Pd(PPh_3)_4$ (10)	1.0	EtOH	1		0		80
6		$Pd(PPh_3)_4$ (10)	1.0	DMF	1		0		75
7	**8a**	$Pd(OAc)_2$ (10)	1.0	MeOH	1	**10a**	91	96:4	9
8		$Pd(OAc)_2$ (10)	1.0	MeOH	2		95	96:4	5
9		$Pd(OAc)_2$ (10)	1.0	MeOH	5		96	97:3	4
10		$Pd(OAc)_2$ (10)	1.2	MeOH	1		95 (87)	95:5	0
11		$Pd(OAc)_2$ (5)	1.2	MeOH	1		79	95:5	17

[a]Determined by ^{19}F NMR. Values in parentheses are isolated yields.

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618–1631

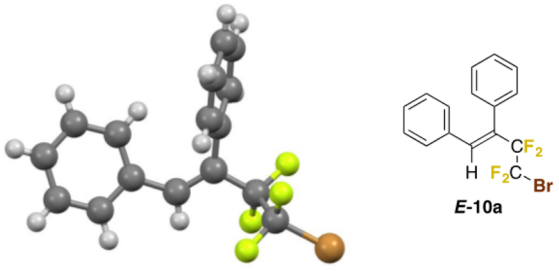
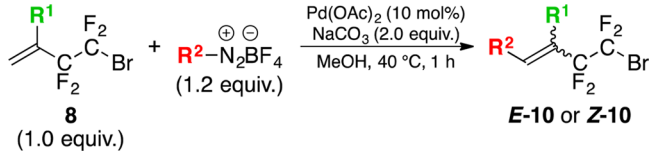


Figure 3. X-ray crystallographic analysis of ***E*-10a**.

yield was quite acceptable (entry 4). A *p*-anisyldiazonium salt, which has a strongly electron-donating group on the benzene ring, led to a significant decrease in the yield, but the stereoselectivity was still high (entry 5). In sharp contrast, aryldiazonium salts having an electron-withdrawing group, such as Cl, CO_2Et, and NO_2, on the benzene ring were significantly effective, providing the desired Heck adducts in excellent yields in a highly stereoselective manner (entries 6–8). Changing an aryl substituent R^1 from Ph to Tol or *p*-AcC_6H_4 did not cause any significant improvement in the reaction efficiency, affording the Heck products **10i,j** in high yields and in a highly stereoselective manner. However, use of the starting **8d** with a

Table 6. Highly Stereoselective Synthesis of Trisubstituted Alkenes Having a Tetrafluoroethylene Fragment via the Heck Reaction of 8

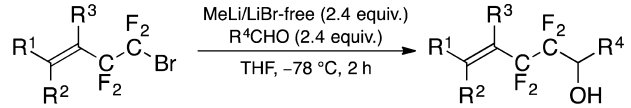


Entry	Major Product	Yield[a]/% [*E*:*Z*][b]	Entry	Major Product	Yield[a]/% [*E*:*Z*][b]
1	***E*-10a**	95 (87) [95:5]	7	***E*-10g**	94 (74) [94:6]
2	***E*-10b**	85 (64) [96:4]	8	***E*-10h**	91 (85) [91:1]
3	***E*-10c**	75 (63) [96:4]	9	***E*-10i**	94 (80) [96:4]
4	***E*-10d**	68 (53) [85:15]	10	***E*-10j**	87 (66) [94:6]
5	***E*-10e**	56 (55) [95:5]	11	***E*-10k**	13 [N.D.[c]]
6	***E*-10f**	93 (76) [93:7]			

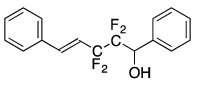
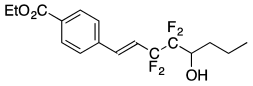
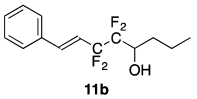
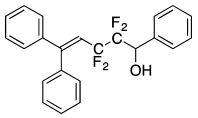
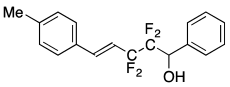
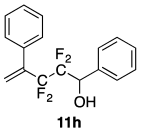
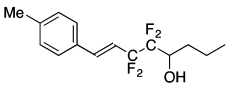
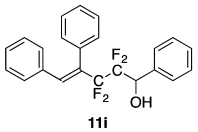
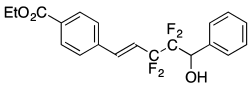
[a]Determined by ^{19}F NMR. Values in parentheses are isolated yields. [b]Values in brackets are the isomeric ratios of *E* and *Z*, which were determined by ^{19}F NMR. [c]Not determined.

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618–1631

Table 7. Reductive Coupling Reactions of Various Multisubstituted Alkenes Having a Tetrafluoroethylene Fragment with Aldehydes



4a, **4b**, **4g**, **5a**, **8a**, **10a** → **11**

Entry	Product	Yield[a]/% of **11**	Entry	Product	Yield[a]/% of **11**
1	 **11a**	90 (72)	6	 **11f**	75 (53)
2	 **11b**	93 (85)	7	 **11g**	75 (61)
3	 **11c**	75 (64)	8	 **11h**	quant. (82)
4	 **11d**	93 (83)	9	 **11i**	85 (72)
5	 **11e**	72 (49)			

[a]Determined by ^{19}F NMR. Values in parentheses are isolated yields.

3-thienyl group as R^1 resulted in a drastic retardation of the reaction, allowing formation of the corresponding Heck product **10k** in only 13% yield. The stereochemistry of major isomers of **10b−i** was determined as *E* on the basis of a reaction mechanism similar to that described in Scheme 1.

Synthetic Application of Multisubstituted Alkenes Having a Tetrafluoroethylene Fragment. In order to open avenues to novel CF_2CF_2-containing organic molecules, we further demonstrated a transformation at a halogen handle in the Heck adducts. As one example for the synthetic application of the Heck adducts **4a**,**b**,**g**, **5a**, **8a**, and **10a**, we performed a reductive coupling reaction with aldehydes according to our previously reported procedure,[5b,c] as described in Table 7. Thus, on treatment of a mixture of 1.0 equiv of **4a** and 2.4 equiv of benzaldehyde with 2.4 equiv of MeLi/LiBr-free in THF at −78 °C for 2 h, the corresponding alcohol **11a** was obtained in 90% yield (entry 1). *n*-Butyraldehyde, in addition to benzaldehyde, could also participate well in the coupling reaction (entry 2). Shifting the starting alkenes from **4a** to **4b** and **4g** also led to satisfactory results, **11c−f** being obtained in 72−93% yields (entries 3−6). As shown in entries 7−9, the substitution pattern at the double bond did not affect the coupling reaction, resulting in the formation of the corresponding alcohols **11g−i** in high to excellent yields.

CONCLUSION

In summary, we have developed a convenient, remarkable, and highly stereoselective synthetic method for the preparation of variously substituted alkenes having a tetrafluoroethylene fragment, which are promising building blocks for novel CF_2CF_2-containing organic molecules. It should be noted that such novel building blocks were easily synthesized from commercially available 4-bromo-3,3,4,4-tetrafluoro-1-butene in several steps through palladium-catalyzed Heck reactions or Suzuki−Miyaura cross-coupling reactions. Additionally,the thus obtained multisubstituted alkenes underwent a smooth reductive coupling reaction with various aldehydes under the influence of MeLi/LiBr-free. Further synthetic applications of these materials are underway in our laboratory, which will be disclosed in the near future.

EXPERIMENTAL SECTION

General Experimental Details. Infrared spectra (IR) were determined in a liquid film on a NaCl plate or as KBr disks. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. ^{19}F NMR (376 MHz) spectra were measured in a chloroform-*d* ($CDCl_3$) solution with trichlorofluoromethane ($CFCl_3$) as an internal standard. ^{19}F NMR was also employed for determining the yield of the products with hexafluorobenzene (C_6F_6).

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631

High-resolution mass spectra (HRMS) experiments were performed with a quadrupole mass spectometer equipped with a FAB ion source.

All reactions were routinely monitored by ^{19}F NMR spectroscopy or TLC and carried out under an atmosphere of argon.

Materials. Methanol was fleshly distilled from magnesium (Mg). A superdehydrated tetrahydrofuran without stabilizer was employed. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin-layer chromatography (TLC) was done with silica gel coated aluminum plates, and 100−200 mesh silica gels were used for the chromatography.

Typical Procedure for the First Heck Reaction of 4-Bromo-3,3,4,4-tetrafluoro-but-1-ene with Various Aryldiazonium Tetrafluoroborates. 4-Bromo-3,3,4,4-tetrafluoro-1-butene (1.04 g, 5.04 mmol) and phenyldiazonium tetrafluoroborate (0.96 g, 5.02 mmol) in methanol (5 mL) was stirred at 40 °C in the presence of $Pd(OAc)_2$ (0.00560 g, 0.025 mmol). After 1 h, the resulting mixture was passed through silica gel and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane only) to give the corresponding (*E*)-1,2-disubstituted alkene **4a** (1.01 g, 3.67 mmol).

*(E)-4-Bromo-3,3,4,4-tetrafluoro-1-phenylbut-1-ene (**4a**).* Colorless oil: yield 73%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.25 (dt, J = 16.1, 11.8 Hz, 1H), 7.21 (dt, J = 16.1, 2.1 Hz, 1H), 7.40−7.45 (m, 3H), 7.48−7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.5 (t, J = 23.9 Hz), 114.7 (tt, J = 252.3, 31.4 Hz), 117.7 (tt, J = 312.0, 42.4 Hz), 127.8, 129.1, 130.3, 133.9, 140.0 (t, J = 8.9 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.14 (t, J = 6.1 Hz, 2F), −109.50 (dt, J = 11.8, 6.1 Hz, 2F); IR (neat) ν 3088, 3065, 3033. 1656, 1338, 1303, 1281, 1237, 1203, 1149, 1080, 972, 915, 760, 718, 689, 661 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_7{}^{79}BrF_4$ $[M]^+$ 281.9667, found 281.9662.

*(E)-4-Bromo-3,3,4,4-tetrafluoro-1-(4-methylphenyl)but-1-ene (**4b**).* Chromatography (silica gel, hexane only) afforded **4b** (0.80 g, 54%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 6.22 (dt, J = 16.1, 11.9 Hz, 1H), 7.19 (dt, J = 16.1, 2.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 113.3 (t, J = 23.9 Hz), 114.8 (tt, J = 252.0, 31.4 Hz), 117.7 (tt, J = 312.0, 42.6 Hz), 127.7, 129.8, 131.1, 139.8 (t, J = 8.9 Hz), 140.6; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.09 (t, J = 6.2 Hz, 2F), −109.31 (dt, J = 11.9, 6.2 Hz, 2F); IR (neat) ν 3584, 3031, 2925, 1657, 1611, 1574, 1515, 1415, 1334, 1304, 1238, 1204 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_9{}^{79}BrF_4$ $[M]^+$ 295.9824, found 295.9820.

*(E)-4-Bromo-3,3,4,4-tetrafluoro-1-(3-methylphenyl)but-1-ene (**4c**).* Chromatography (silica gel, hexane only) afforded **4c** (0.56 g, 37%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 6.28 (dt, J = 16.2, 11.8 Hz, 1H), 7.21 (dt, J = 16.2, 2.0 Hz, 1H), 7.25−7.28 (m, 1H), 7.31−7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 114.2 (t, J = 23.9 Hz), 114.8 (tt, J = 252.2, 31.4 Hz), 117.7 (tt, J = 312.6, 43.0 Hz), 125.0, 128.4, 129.0, 131.1, 133.8, 138.8, 140.1 (t, J = 8.8 Hz); ^{19}F NMR (400 MHz, $CDCl_3$) δ −66.11 (t, J = 6.2 Hz, 2F), −109.44 (dt, J = 11.8, 6.2 Hz, 2F); IR (neat) ν 3444, 3030, 2925, 2860, 1656, 1231, 1150, 1111,1080, 1056, 972, 916 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_9{}^{79}BrF_4$ $[M]^+$ 295.9824, found 295.9821.

*(E)-4-Bromo-3,3,4,4-tetrafluoro-1-(2-methylphenyl)but-1-ene (**4d**).* Chromatography (silica gel, hexane only) afforded **4d** (0.54 g, 36%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 3H), 6.19 (dt, J = 16.2, 11.8 Hz, 1H), 7.25−7.29 (m, 2H), 7.32−7.36 (m, 1H), 7.51 (dt, J = 16.2, 2.2 Hz, 1H), 7.51−7.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 114.6 (tt, J = 252.4, 31.4 Hz), 115.8 (t, J = 23.8 Hz), 117.6 (tt, J = 312.3, 42.2 Hz), 126.4, 126.6, 130.0, 130.9, 133.1, 137.1, 138.0 (t, J = 8.9 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.20 (t, J = 6.2 Hz, 2F), −109.5 (dt, J = 11.8, 6.2 Hz, 2F); IR (neat) ν 3415, 3067, 3038, 2945, 1654, 1238, 1149, 1081, 1058, 972, 915, 753 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_9{}^{79}BrF_4$ $[M]^+$ 295.9824, found 295.9833.

*(E)-4-Bromo-1-(4-chlorophenyl)-3,3,4,4-tetrafluorobut-1-ene (**4f**).* Chromatography (silica gel, hexane only) afforded **4f** (1.46 g, 88%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (dt, J = 16.1, 11.7 Hz, 1H), 7.15 (dt, J = 16.1, 2.2 Hz, 1H), 7.36−7.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.2 (tt, J = 263.0, 32.0 Hz), 115.1 (t, J = 23.5 Hz), 117.5 (tt, J = 311.6, 42.6 Hz), 128.9, 129.3, 132.3, 136.2, 138.7 (t, J = 8.9 Hz); ^{19}F NMR (400 MHz, $CDCl_3$ $CFCl_3$) δ −66.20 (t, J = 6.3 Hz, 2F), −109.59 (dt, J = 11.7, 6.3 Hz, 2F); IR (neat) ν 1903, 1658, 1595, 1493, 1408, 1303, 1240, 1150, 1083, 1056, 973, 916, 809, 741 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_6{}^{79}Br^{35}ClF_4$ $[M^+]$ 315.9278, found 315.9273.

*(E)-Ethyl 4-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-1-yl)benzoate (**4g**).* Chromatography (silica gel, hexane/ethyl acetate 20/1) afforded **4g** (1.58 g, 88%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (t, J = 7.1 Hz, 3H), 4.39 (q, J = 7.1 Hz, 2H), 6.32 (dt, J = 16.1, 11.6 Hz, 1H), 7.21 (dt, J = 16.1, 2.0 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 8.06 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 61.3, 114.3 (tt, J = 252.5, 31.7 Hz), 116.7 (t, J = 24.0 Hz), 117.3 (tt, J = 311.9, 42.1 Hz), 127.6, 130.2, 131.8, 137.8, 138.9 (t, J = 8.9 Hz), 165.9; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.20 (t, J = 6.2 Hz, 2F), −109.75 (dt, J = 11.6, 6.2 Hz, 2F); IR (neat) ν 2984, 2907, 1719, 1658, 1610, 1573, 1415, 1368, 1280, 1205, 1082, 976, 864, 730 cm^{-1}; HRMS (FAB+) calcd for $C_{13}H_{12}{}^{79}BrF_4O_2$ $[M + H]^+$ 354.9957, found 354.9971.

*(E)-4-Bromo-3,3,4,4-tetrafluoro-1-(4-nitrophenyl)but-1-ene (**4h**).* Chromatography (silica gel, hexane/ethyl acetate 10/1) afforded **4h** (1.42 g, 87%) as a yellow solid: mp 91.9−92.3 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.26 (dt, J = 16.2, 11.4 Hz, 1H), 7.26 (dt, J = 16.2, 2.1 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 8.27 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.0 (tt, J = 252.9, 31.9 Hz), 117.1 (tt, J = 312.4, 41.6 Hz), 119.0 (t, J = 24.2 Hz), 124.4, 128.5, 137.7 (t, J = 8.4 Hz), 139.8, 148.6; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.32 (t, J = 6.2 Hz, 2F), −110.10 (dt, J = 11.4, 6.2 Hz, 2F); IR (KBr) ν 3109, 3085, 2940, 2849, 2728, 2452, 1934, 1799, 1514, 1348, 1235, 1075, 905 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_7{}^{79}BrNF_4O_2$ $[M + H]^+$ 327.9596, found 327.9599.

Typical Procedure for the Heck Reaction of Various (*E*)-1,2-Disubstituted Alkenes with Various Aryldiazonium Tetrafluoroborates. (*E*)-4-Bromo-1-phenyl-3,3,4,4-tetrafluoro-but-1-ene (**4a**; 0.087 g, 0.31 mmol) and phenyldiazonium tetrafluoroborate (0.19 g, 0.99 mmol) in methanol (0.6 mL) was stirred at 40 °C in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (0.031 g, 0.030 mmol) and P(*o*-Tol)$_3$ (0.037 g, 0.12 mmol). After 24 h, the resulting mixture was passed through silica gel and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane only) to give the corresponding trisubstituted alkene **5a** (0.08 g, 0.22 mmol).

*4-Bromo-3,3,4,4-tetrafluoro-1,1-diphenylbut-1-ene (**5a**).* Yellow oil: yield 73%; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (t, J = 14.3 Hz, 1H), 7.25−7.30 (m, 4H), 7.32−7.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.0 (t, J = 21.7 Hz), 114.1 (tt, J = 249.1, 31.0 Hz), 117.9 (tt, J = 312.4, 41.3 Hz), 128.0, 128.1, 128.4, 128.6, 129.2, 129.6, 137.7, 140.9, 154.4 (t, J = 4.2 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.17 (t, J = 6.9 Hz, 2F), −101.92 (dt, J = 14.3, 6.9 Hz, 2F); IR (neat) ν 3090, 3060, 3016, 1636, 1493, 1446, 1227, 1145, 1078, 906, 885, 698 cm^{-1}. HRMS (FAB+) calcd for $C_{16}H_{11}{}^{79}BrF_4$ $[M]^+$ 357.9980, found 357.9975.

*4-Bromo-3,3,4,4-tetrafluoro-1-(4-methylphenyl)-1-phenylbut-1-ene (**5b**).* In the reaction with **4a** as a substrate, chromatography (silica gel, hexane only) afforded **5b** (84 mg, 75%) as a colorless oil: isomeric ratio E/Z = 80/20; IR (neat) ν 3035, 2924, 1634, 1510, 1445, 1228, 1133, 1050, 886 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}BrF_4$ $[M]^+$ 372.0137, found 372.0143. **5b** was also obtained in 90% isolated yield (96 mg) as a 26/74 E/Z mixture, through the Heck reaction of **4b** with phenyldiazonium salt: IR (neat) ν 3038, 2925 1634, 1371, 1227, 1144, 1079, 1051, 907, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}{}^{79}BrF_4$ $[M]^+$ 372.0137, found 372.0139.

***E*-5b**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 6.16 (t, J = 14.3 Hz, 1H), 7.16−7.55 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 112.0 (t, J = 21.7 Hz), 114.2 (tt, J = 254.1, 31.3 Hz), 118.0 (tt, J = 312.8, 41.6 Hz), 127.9, 128.0, 128.3, 129.0−129.2 (m, 2C), 129.3, 137.9, 139.8, 154.2 (t, J = 4.1 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.10 (t, J = 7.0 Hz, 2F), −101.66 (dt, J = 14.3, 7.0 Hz, 2F).

***Z*-5b**: ^1H NMR (400 MHz, $CDCl_3$) δ 2.4 (s, 3H), 6.14 (t, J = 14.3 Hz, 1H), 7.18−7.43 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 112.7 (t, J = 21.5 Hz), 114.2 (tt, J = 244.5, 30.9 Hz), 118.0 (tt, J =

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631

312.8, 41.6 Hz) 128.2, 128.6, 128.7, 129.1−129.2 (m, 2C), 129.5, 138.3, 141.3, 154.6 (t, J = 4.1 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.16 (t, J = 7.2 Hz, 2F), −101.73 (dt, J = 14.3, 7.2 Hz, 2F).

*4-Bromo-3,3,4,4-tetrafluoro-1-(3-methylphenyl)-1-phenylbut-1-ene (**5c**).* Chromatography (silica gel, hexane only) afforded **5c** (39 mg, 34%) as a colorless oil: isomeric ratio E/Z = 83/17; IR (neat) ν 3027, 2924, 1636, 1604, 1493, 1445, 1233, 1151, 1080, 906, 774, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}{}^{79}BrF_4$ $[M]^+$ 372.0137, found 372.0139.

***E*-5c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.10 (t, J = 14.3 Hz, 1H), 7.03−7.41 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 112.7 (t, J = 21.7 Hz), 114.0 (tt, J = 254.2, 30.8 Hz) 117.8 (tt, J = 312.8, 41.3 Hz), 127.8, 127.9, 128.2, 128.5, 129.0, 130.2, 137.7, 138.2, 140.8, 141.4, 154.4 (t, J = 3.8 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.13 (t, J = 6.8 Hz, 2F), −101.86 (dt, J = 14.3, 6.8 Hz, 2F).

***Z*-5c** (only one signal which could be identified was analyzed): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 112.7 (t, J = 21.6 Hz), 124.3, 125.2, 128.0, 128.4, 128.6, 129.1, 137.5, 137.5, 138.3, 140.9, 154.4 (t, J = 3.5 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.16 (t, J = 6.7 Hz, 2F), −101.95 (dt, J = 14.3, 6.7 Hz, 2F).

*4-Bromo-3,3,4,4-tetrafluoro-1-(4-methoxyphenyl)-1-phenylbut-1-ene (**5e**).* Chromatography (silica gel, hexane/ethyl acetate 20/1) afforded **5e** (27 mg, 23%) as a yellow oil: isomeric ratio E/Z = 86/14; IR (neat) ν 3054, 2933, 2831, 1726, 1605, 1512, 1294, 1253, 1145, 1078, 1050, 907, 828, 701 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}{}^{79}BrF_4O$ $[M]^+$ 388.0086, found 388.0097.

***E*-5e**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.05 (t, J = 14.3 Hz, 1H), 6.84 (d, J = 8.8 Hz, 2H), 7.17−7.39 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 110.9 (t, J = 21.7 Hz), 113.4, 114.0, 114.3 (tt, J = 254.1, 30.8 Hz), 118.0 (tt, J = 313.0, 41.7 Hz), 127.9, 128.3, 129.2 (t, J = 2.5 Hz), 129.5, 138.0, 142.5 (t, J = 4.1 Hz), 153.7 (t, J = 4.1 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.07 (t, J = 7.0 Hz, 2F), −101.43 (dt, J = 14.3, 7.0 Hz, 2F).

***Z*-5e** (only signals which could be identified were analyzed): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.91 (d, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 112.5 (t, J = 21.5 Hz), 113.7, 128.6, 129.0, 130.8 (t, J = 2.9 Hz), 131.0, 141.6, 154.3 (t. J = 4.2 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.21 (t, J = 7.1 HZ, 2F), −101.58 (dt, J = 14.3, 7.1 Hz, 2F).

*4-Bromo-1-(4-chlorophenyl)-3,3,4,4-tetrafluoro-1-phenylbut-1-ene (**5f**).* Chromatography (silica gel, hexane only) afforded **5f** (99 mg, 78%) as a white solid: mp 65.2−66.8 °C; isomeric ratio E/Z = 96/4.

***E*-5f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (t, J = 14.1 Hz, 1H), 7.18−7.41 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.3 (t, J = 21.9 Hz), 113.6 (tt, J = 254.5, 31.0 Hz), 117.8 (tt, J = 313.0, 41.3 Hz), 128.1, 128.7, 128.9, 129.1 (t, J = 2.4 Hz), 129.4, 135.8, 137.2, 139.4, 153.2 (t, J = 4.1 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.24 (t, J = 6.7 Hz, 2F), −102.04 (dt, J = 14.1, 6.7 Hz, 2F); IR (KBr) ν 3081, 3055, 3022, 2995, 2926, 2379, 1964, 1644, 1589, 1494 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{10}{}^{79}Br^{35}ClF_4$ $[M]^+$ 391.9591, found 391.9592.

*X-ray Structural Analysis of **E**-5f.* A colorless prismiatic crystal of ***E*-5f** having approximate dimensions 0.47 × 0.34 × 0.30 mm was mounted on a glass fiber. All measurements were made on a diffractometer with filtered Mo Kα radiation and a rotating anode generator. Compound ***E*-5f**: triclinic, a = 5.3972(4) Å, b = 9.9775(7) Å, c = 14.1887(10) Å, α = 97.739(7)°, β = 93.504(7)°, γ = 99.049(7)°, V = 745.03(8) Å^3, T = 293 K, space group $P\bar{1}$ (No. 2), Z = 1, μ(Mo Kα) = 0.71075 mm^{-1}, 3394 reflections measured, 3063 unique reflections, which were used in all calculations. The final R1 and wR2 values were 0.029 and 0.070 ($I > 2\sigma(I)$). All calculations were performed by using the CrystalStructure crystallographic software package. The structure was solved by direct methods and expanded using Fourier techniques. The goodness of fit indicator was 1.060. Crystallographic data for this compound have been deposited with the Cambridge Crystallographic Data Centre as supplementary data no. CCDC 1515843. Copies of the data can be obtained free of charge by applying to The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (https://summary.ccdc.cam.ac.uk/structure-summary-form).

***Z*-5f** (only signals which could be identified were analyzed): ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.6 (t, J = 11.7 Hz), 113.6 (tt, J = 254.5, 31.0 Hz), 117.8 (tt, J = 313.0, 41.3 Hz), 128.1, 128.3, 128.7, 129.8, 130.6 (t, J = 2.6 Hz), 134.6, 136.1, 139.4, 153.2 (t, J = 4.2 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.27 (t, J = 6.9 Hz, 2F), −101.85 (dt, J = 14.1, 6.9 Hz, 2F).

*Ethyl 4-[(4-Bromo-3,3,4,4-tetrafluoro-1-phenyl)but-1-en-1-yl]-benzoate (**5g**).* In the reaction with **4a** as a substrate, chromatography (silica gel, hexane/ethyl acetate 10/1) afforded **5g** (100 mg, 76%) as a colorless oil: isomeric ratio E/Z = 99/1. **5g** was also obtained as an E/Z mixture of 3/97, through the Heck reaction of **4g** with phenyldiazonium salt: IR (neat) ν 3054, 2961, 1717, 1637, 1444, 1272, 1145, 1105, 1080, 1051, 908, 773, 701 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{16}{}^{79}BrF_4O_2$ $[M + H]^+$ 431.0270, found 431.0269.

***E*-5g**: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3H), 4.38 (q, J = 7.1 Hz, 2H), 6.18 (t, J = 14.0 Hz, 1H), 7.22−7.41 (m, 7H), 8.00 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 61.3, 113.9 (tt, J = 254.8, 30.9 Hz), 114.6 (t, J = 21.9 Hz), 117.7 (tt, J = 313.1, 40.1 Hz) 128.0, 128.1, 128.7, 129.1, 129.8, 131.4, 137.1, 145.1, 153.5 (t, J = 3.9 Hz), 166.1; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.25 (t, J = 6.8 Hz, 2F), −102.2 (dt, J = 14.0, 6.8 Hz, 2F).

***Z*-5g**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.1 Hz, 3H), 4.40 (q, J = 7.1 Hz, 2H), 6.17 (t, J = 14.2 Hz, 1H), 7.20−7.24 (m, 2H), 7.31−7.39 (m, 5H), 8.07 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 61.3, 113.7 (t, J = 22.1 Hz), 114.3 (tt, J = 286.1, 31.3 Hz), 117.7 (tt, J = 312.8, 41.3 Hz), 127.9, 128.8, 129.0, 129.2 (t, J = 2.5 Hz), 130.3, 130.5, 131.0, 140.0, 142.3, 166.4; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.21 (t, J = 6.9 Hz, 2F), −102.1 (dt, J = 14.2, 6.9 Hz, 2F).

*4-Bromo-3,3,4,4-tetrafluoro-1-(4-nitrophenyl)-1-phenylbut-1-ene (**5h**).* Chromatography (silica gel, hexane/ethyl acetate 20/1) afforded **5h** (88 mg, 67%) as a yellow oil: isomeric ratio E/Z = 99:1; IR (neat) ν 3082, 2850, 1602, 1522, 1348, 1228, 1145, 1081, 1052, 909, 701 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{11}{}^{79}BrF_4NO_2$ $[M + H]^+$ 403.9909, found 403.9907.

***E*-5h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (t, J = 14.1 Hz, 1H), 7.23−7.25 (m, 2H), 7.42−7.45 (m, 5H), 8.18−8.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.6 (tt, J = 255.5, 31.4 Hz), 116.1 (t, J = 22.0 Hz), 117.5 (tt, J = 312.9, 40.8 Hz), 123.3, 123.8, 128.4, 129.0 (t, J = 4.0 Hz), 130.2, 136.4, 146.9, 148.3, 152.4 (t, J = 3.7 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.38 (t, J = 6.8 Hz, 2F), −102.61 (dt, J = 14.1, 6.8 Hz, 2F).

***Z*-5h** (only signals which could be identified were analyzed): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (t, J = 13.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.6, 125.1, 128.5, 129.4, 132.7, 134.7, 139.2, 144.4, 147.9, 152.0 (t, J = 4.6 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −66.38 (t, J = 6.8 Hz, 2F), −102.03 (dt, J = 13.8, 6.8 Hz, 2F).

Bromination of 4-Bromo-3,3,4,4-tetrafluorobut-1-ene. To a solution of 4-bromo-3,3,4,4-tetrafluorobut-1-ene (41.4 g, 200.2 mmol) in dichloromethane (200 mL) was added bromine dropwise (11 mL). The solution was stirred at room temperature overnight. The reaction mixture was quenched with $NaHCO_3$(aq) and $Na_2S_2O_3$(aq) and extracted with dichloromethane three times. The organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane only) to give the brominated compound (68.7 g, 94%).

*1,2,4-Tribromo-3,3,4,4-tetrafluorobutane (**6**).* Colorless oil: yield 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (dd, J = 11.8, 9.1 Hz, 1H), 4.02 (dd, J = 11.8, 3.5 Hz, 1H), 4.55 (dddd, J = 12.5, 11.4, 9.1, 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7−29.9 (m), 46.5 (t, J = 25.3 Hz), 113.6 (ddt, J = 261.9, 260.4, 30.9 Hz), 116.5 (tt, J = 314.0, 39.8 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −61.59 (dd, J = 178.9, 6.1 Hz, 1F), −62.12 (dt, J = 178.9, 3.9 Hz, 1F), −107.89 to −107.13 (m, 1F), −109.92 (ddd, J = 264.4, 11.4, 3.9 Hz, 1F); IR (neat) ν 1430, 1328, 1262, 1241, 1151, 1102, 1078, 1044, 916, 891, 859, 830, 778, 607 cm^{-1}; MS (FAB) m/z 155 ($CF_2CBrC^+H_2$, 56), 77 ($CF_2CHC^+H_2$, 40).

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631

Debromination of 1,2,4-Tribromo-3,3,4,4-tetrafluorobutane with NaOH(aq). NaOH (30.2 g, 754.3 mmol) was dissolved in H_2O (63 mL). NaOH(aq) was added to 1,2,4-tribromo-3,3,4,4-tetrafluorobutane (68.6 g, 187.1 mmol), and the mixture was stirred at room temperature for 24 h. The whole mixture was extracted. The organic layer was dried over anhydrous Na_2SO_4 and filtered to give the dibromo compound (48.4 g, 90% yield).

*2,4-Dibromo-3,3,4,4-tetrafluorobut-1-ene (**7**).* Colorless oil: yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (dt, J = 3.0, 1.3 Hz, 1H), 6.54 (d, J = 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 110.8 (tt, J = 257.6, 31.6 Hz), 115.9 (tt, J = 313.9, 42.3 Hz), 116.1 (t, J = 29.4 Hz), 127.6 (t, J = 5.9 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −63.42 (t, J = 4.9 Hz, 2F), −105.99 (t, J = 4.9, 2F); IR (neat) ν 1627, 1398, 1239, 1158, 1102, 1064, 1040, 934, 910, 870, 758, 681, 472 cm^{-1}; MS (FAB) m/z 57 ($FCCC^+H_2$, 65), 155 ($CF_2CBrC^+H_2$, 38), 77 ($CF_2CHC^+H_2$, 34).

General Procedure for the Synthesis of 8a via a Suzuki–Miyaura Cross-Coupling Reaction. A sealed tube was charged with **7** (2.00 g, 7.0 mmol), $PhB(OH)_2$ (1.71 g, 14 mmol), $Pd(PPh_3)_4$ (0.406 g, 5 mol %), Na_2CO_3 (1.44 g, 14 mmol), toluene (7.20 mL), and H_2O (2.8 mL). The mixture was stirred at 80 °C under argon for 1 h. The mixture was diluted with ethyl ether and washed with water and then dried over anhydrous sodium sulfate and evaporated in vacuo. **8a** was purified by silica gel column chromatography (1.28 g, 4.51 mmol, 62%).

*4-Bromo-3,3,4,4-tetrafluoro-2-phenylbut-1-ene (**8a**).* Yellow oil: yield 62%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (t, J = 1.7 Hz, 1H), 6.04 (s, 1H), 7.38–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.5 (tt, J = 256.1, 31.3 Hz), 117.8 (tt, J = 313.8, 43.2 Hz), 125.6 (t, J = 8.3 Hz), 128.4, 128.7, 128.9, 135.5, 138.7 (t, J = 22.2 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −63.15 (t, J = 5.5 Hz, 1F), −107.11 (t, J = 5.5 Hz, 2F); IR (neat) ν 3053, 2941, 1495, 1318, 1244, 1150, 1092, 907, 876, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{10}H_7{}^{79}BrF_4$ $[M]^+$ 281.9667, found 281.9675.

*4-Bromo-3,3,4,4-tetrafluoro-2-(4-methylphenyl)but-1-ene (**8b**).* Chromatography (silica gel, hexane only) afforded **8b** (0.45 g, 75%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 5.78 (t, J = 1.5 Hz, 1H), 5.99 (s, 1H), 7.18 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 114.6 (tt, J = 256.0, 31.1 Hz), 117.9 (tt, J = 314.0, 43.2 Hz), 125.0 (t, J = 8.2 Hz), 128.7, 129.1, 132.6, 138.6 (t, J = 21.5 Hz), 138.8; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −63.10 (t, J = 5.5 Hz, 2F), −107.07 (t, J = 5.5 Hz, 2F); IR (neat) ν 3020, 2925, 1514, 1238, 1152, 1090, 1046, 1022, 946, 907, 876, 826 cm^{-1}; HRMS (FAB+) calcd for $C_{11}H_9{}^{79}BrF_4$ $[M]^+$ 295.9824, found 295.9835.

*4-(4-Bromo-3,3,4,4-tetrafluorobut-1-en-2-yl)phenyl methyl ketone (**8c**).* Chromatography (silica gel, hexane/ethyl acetate 10/1) afforded **8c** (0.54 g, 78%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 5.85 (t, J = 1.6 Hz, 1H), 6.09 (s, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5, 114.2 (tt, J = 256.5, 31.4 Hz), 117.4 (tt, J = 313.3, 42.7 Hz), 126.6 (t, J = 8.2 Hz), 128.3, 129.0, 137.1, 137.7 (t, J = 22.4 Hz), 139.8, 197.4; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −107.18 (t, J = 5.6 Hz, 2F), −63.45 (t, J = 5.6 Hz, 2F); IR (neat) ν 3359, 3006, 1687, 1607, 1561, 1404, 1360, 1267, 1152, 1092, 1046, 909 cm^{-1}; HRMS (FAB+) calcd for $C_{12}H_{10}{}^{79}BrF_4O$ $[M + H]^+$ 324.9851, found 324.9824.

*4-Bromo-3,3,4,4-tetrafluoro-2-(3-thienyl)but-1-ene (**8d**).* Chromatography (silica gel, hexane only) afforded **8d** (0.13 g, 23%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1H), 5.94 (t, J = 1.8 Hz, 1H), 7.18 (dd, J = 5.1, 1.0 Hz, 1H), 7.31 (dd, J = 5.1, 3.0 Hz, 1H), 7.38–7.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.6 (tt, J = 255.8, 31.7 Hz), 117.8 (tt, J = 313.5, 45.6 Hz), 123.5 (t, J = 8.5 Hz), 124.6, 125.7, 127.5, 133.3 (t, J = 22.9 Hz), 135.0; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −63.57 (t, J = 4.9 Hz, 2F), −107.30 (t, J = 4.9 Hz, 2F); IR (neat) ν 3128, 2933, 1626, 1399, 1235, 1147, 1090, 1045, 930, 903, 863, 832, 793, 752, 671 cm^{-1}; HRMS (FAB+) calcd for $C_8H_5{}^{79}BrF_4S$ $[M]^+$ 287.9231, found 287.9244.

Heck Reaction of (*E*)-2,2-Disubstituted Alkenes with Various Aryldiazonium Tetrafluoroborates. 4-Bromo-3,3,4,4-tetrafluoro-1,2-diphenylbut-1-ene (**8a**; 0.08 g, 0.27 mmol) and phenyldiazonium tetrafluoroborate (0.69 g, 0.36 mmol) in methanol (0.30 mL) was stirred at 40 °C in the presence of $Pd(OAc)_2$ (0.00677 g, 0.030 mmol). After 1 h, the resulting mixture was passed through silica gel and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane only) to give the corresponding (*E*)-1,2-disubstituted alkene **10b** (0.09 g, 0.24 mmol, 87% yield, *E*/*Z* = 95/5).

*4-Bromo-3,3,4,4-tetrafluoro-1,2-diphenylbut-1-ene (**10a**).* White solid: mp 70.0–70.8 °C; yield 87%.

***E*-10a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–7.02 (m, 2H), 7.17–7.24 (m, 3H), 7.25–7.35 (m, 3H), 7.40–7.43 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.6 (tt, J = 287.4, 33.1 Hz), 118.3 (tt, J = 314.0, 44.9 Hz), 128.4, 128.8, 128.9, 129.1, 129.5 (t, J = 20.9 Hz), 130.3, 130.6, 133.4, 134.0, 137.2 (t, J = 8.9 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.24 (t, J = 5.6 Hz, 2F), −106.11 (t, J = 5.6 Hz, 2F); IR (KBr) ν 3054, 2927, 2855, 2345, 1957, 1895, 1813, 1774, 1727, 1641, 1576, 1495 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{11}{}^{79}BrF_4$ $[M]^+$ 357.9980, found 357.9982.

*X-ray Structural Analysis of **E-10a**.* A colorless prismic crystal of ***E*-10a** having approximate dimensions of 0.30 × 0.21 × 0.20 mm was mounted on a glass fiber. All measurements were made on a diffractometer with filtered Mo Kα radiation and a rotating anode generator. Compound ***E*-10a**: triclinic, a = 5.7440(2) Å, b = 9.8680(2) Å, c = 26.1249(6) Å, α = 89.552(2)°, β = 84.710(2)°, γ = 76.664(2)°, V = 1434.60(7) Å^3, T = 173(2) K, space group $P\bar{1}$ (No. 2), Z = 4, μ(Mo Kα) = 0.71075 mm^{-1}, 5318 reflection measured, 4385 unique reflections, which were used in all calculations. The final R1 and wR2 values were 0.030 and 0.065 ($I > 2\sigma(I)$). All calculations were performed by using the CrystalStructure crystallographic software package. The structure was solved by direct methods and expanded using Fourier techniques. The goodness of fit indicator was 1.011. Crystallographic data for this compound have been deposited with the Cambridge Crystallographic Data Centre as supplementary data no. CCDC 1515844. Copies of the data can be obtained free of charge by applying to The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (https://summary.ccdc.cam.ac.uk/structure-summary-form).

*4-Bromo-3,3,4,4-tetrafluoro-1-(4-methylphenyl)-2-phenylbut-1-ene (**10b**).* Chromatography (silica gel, hexane only) afforded **10b** (98 mg, 64%, *E*/*Z* = 96/4) as a white solid: mp 81.7–81.9 °C.

***E*-10b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 6.84 (d, J = 8.1 Hz, 2H), 6.96 (d, J = 8.1 Hz, 2H), 7.19 (s, 1H), 7.27–7.28 (m, 2H), 7.36–7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 114.7 (tt, J = 256.1, 30.6 Hz), 118.4 (tt, J = 313.5, 44.8 Hz), 128.4 (t, J = 21.3 Hz), 128.7, 128.9, 129.1, 130.3, 130.6, 131.2, 133.6, 137.1 (t, J = 8.7 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.18 (t, J = 5.6 Hz, 2F), −105.9 (t, J = 5.6 Hz, 2F); IR (KBr) ν 3054, 3031, 3020, 2924, 2862, 2379, 1964, 1908, 1638, 1607, 1727, 1511, 1458 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}{}^{79}BrF_4$ $[M]^+$ 372.0137, found 372.0141.

*4-Bromo-3,3,4,4-tetrafluoro-1-(3-methylphenyl)-2-phenylbut-1-ene (**10c**).* Chromatography (silica gel, hexane only) afforded **10c** (92 mg, 63%, *E*/*Z* = 96/4) as a white solid: mp 48.9–49.4 °C.

***E*-10c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 6.77 (d, J = 3.6 Hz, 1H), 6.85 (s, 1H), 7.06 (t, J = 5.0 Hz, 2H), 7.26–7.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 114.7 (tt, J = 256.5, 30.5 Hz), 118.4 (tt, J = 313.9, 45.1 Hz), 127.2, 128.2, 128.7, 128.8, 129.2 (t, J = 21.5 Hz), 129.8, 130.6, 131.3, 133.5, 133.9, 137.3 (t, J = 8.6 Hz), 137.9; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.21 (t, J = 5.7 Hz, 2F), −106.1 (t, J = 5.7 Hz, 2F); IR (KBr) ν 3053, 3025, 2952, 2921, 2861, 2735, 2379, 2304, 2238, 1946, 1879 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}{}^{79}BrF_4$ $[M]^+$ 372.0137, found. 372.0145.

*4-Bromo-3,3,4,4-tetrafluoro-1-(2-methylphenyl)-2-phenylbut-1-ene (**10d**).* Chromatography (silica gel, hexane only) afforded **10d** (79 mg, 53%, *E*/*Z* = 85/15) as a yellow oil.

***E*-10d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 6.70 (d, J = 7.5 Hz, 1H), 6.86 (t, J = 7.5 Hz, 1H), 7.10 (td, J = 7.5, 0.9 Hz, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.19–7.31 (m, 5H), 7.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 114.8 (tt, J = 256.9, 30.4 Hz), 118.3 (tt, J = 314.2, 44.4 Hz), 125.5, 128.37, 128.44, 129.4, 130.0, 130.1, 130.6 (t, J

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618–1631

= 20.9 Hz), 130.7, 133.1, 133.6, 136.8 (t, J = 8.7 Hz), 137.2; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.74 (t, J = 6.0 Hz, 2F), −106.36 (t, J = 6.0 Hz, 2F); IR (neat) ν 3063, 3035, 1643, 1444, 1228, 1161, 1077, 958, 799, 725, 698 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}{}^{79}BrF_4$ $[M]^+$ 372.0137, found 372.0136.

*4-Bromo-3,3,4,4-tetrafluoro-1-(4-methoxyphenyl)-2-phenylbut-1-ene (**10e**).* Chromatography (silica gel, hexane/ethyl acetate 30:1) afforded **10e** (89 mg, 55%, E/Z = 95/5) as a white solid: mp 94.9−95.5 °C.

***E*-10e**:^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.68 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 7.16 (s, 1H), 7.28−7.30 (m, 2H), 7.38−7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 113.8, 114.8 (tt, J = 256.4, 30.8 Hz), 118.5 (tt, J = 314.0, 45.6 Hz), 126.6, 126.9 (t, J = 23.5 Hz), 128.7, 129.0, 130.7, 131.9, 133.7, 136.5 (t, J = 8.7 Hz), 160.2; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.11 (t, J = 5.7 Hz, 2F), −105.7 (t, J = 5.7 Hz, 2F); IR (KBr) ν 3033, 2969, 2939, 2844, 2558, 2516, 2049, 1967, 1892, 1637, 1602 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}{}^{79}BrF_4O$ $[M]^+$ 388.0086, found 388.0084.

*4-Bromo-1-(4-chlorophenyl)-3,3,4,4-tetrafluoro-2-phenylbut-1-ene (**10f**).* Chromatography (silica gel, hexane only) afforded **10f** (0.11 g, 76%, E/Z = 93/7) as a white solid: mp 100.0−100.8 °C.

***E*-10f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H), 7.18 (s, 1H), 7.24−7.26 (m, 2H), 7.36−7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.5 (tt, J = 251.5, 30.9 Hz), 118.2 (tt, J = 313.8, 44.9 Hz), 128.6, 129.02, 129.04, 130.2 (t, J = 21.5 Hz), 130.5, 131.4, 132.5, 133.0, 135.0, 135.8 (t, J = 8.8 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.32 (t, J = 5.7 Hz, 2F), −106.3 (t, J = 5.7 Hz, 2F); IR (KBr) ν 3059, 2925, 2372, 2292, 1964, 1907, 1820, 1774, 1639, 1589, 1494, 1443, 1407, 1306, 1281 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{10}{}^{79}Br^{35}ClF_4$ $[M]^+$ 391.9591, found 391.9591.

*Ethyl 4-(4-Bromo-3,3,4,4-tetrafluoro-2-phenylbut-1-en-1-yl)-benzoate (**10g**).* Chromatography (silica gel, hexane/ethyl acetate 20/1) afforded **10g** (0.13 g, 74%, E/Z = 94/6) as a white solid: mp 75.1−76.4 °C.

***E*-10g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, J = 7.1 Hz, 3H), 4.33 (q, J = 7.1 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H), 7.23−7.27 (m, 3H), 7.34−7.40 (m, 3H), 7.82 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 61.1, 114.4 (tt, J = 252.3, 31.0 Hz), 118.1 (tt, J = 314.7, 44.4 Hz), 128.9, 129.0, 129.4, 130.0, 130.4, 130.5, 131.8 (t, J = 24.5 Hz), 132.8, 136.2 (t, J = 8.8 Hz), 138.3, 166.0; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.39 (t, J = 5.5 Hz, 2F), −106.5 (t, J = 5.5 Hz, 2F); IR (KBr) ν 3406, 3062, 2983, 2942, 2928, 2872, 2379, 2294, 2143, 1927, 1710 cm^{-1}; HRMS (FAB+) calcd for $C_{19}H_{16}{}^{79}BrF_4O_2$ $[M + H]^+$ 431.0270, found 431.0268.

*4-Bromo-3,3,4,4-tetrafluoro-1-(4-nitrophenyl)-2-phenylbut-1-ene (**10h**).* Chromatography (silica gel, hexane/ethyl acetate 20/1) afforded **10h** (0.14 g, 85%, E/Z = 91/1) as a yellow solid: mp 89.8−90.0 °C.

***E*-10h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 8.9 Hz, 2H), 7.23 (d, J = 7.0 Hz, 2H), 7.36 (s, 1H), 7.36−7.44 (m, 3H), 8.00 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 114.2 (tt, J = 257.7, 31.0 Hz), 117.8 (tt, J = 314.0, 44.0 Hz), 123.5, 129.2, 129.5, 130.3, 130.8, 132.2, 133.8 (t, J = 21.7 Hz), 134.9 (t, J = 8.9 Hz), 140.5, 147.5; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.55 (t, J = 5.8 Hz, 2F), −106.87 (t, J = 5.8 Hz, 2F); IR (KBr) ν 3109, 3077, 2935, 2856, 2455, 2370, 1974, 1587, 1502, 1419 cm^{-1}; HRMS (FAB+) calcd for $C_{16}H_{11}{}^{79}BrF_4NO_2$ $[M + H]^+$ 403.9909, found 403.9907.

*4-Bromo-3,3,4,4-tetrafluoro-2-(4-methylphenyl)-1-phenylbut-1-ene (**10i**).* Chromatography (silica gel, hexane only) afforded **10i** (0.12 g, 80%, E/Z = 96/4) as a colorless oil.

***E*-10i**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.02 (d, J = 7.1 Hz, 2H), 7.16−7.25 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 114.7 (tt, J = 256.5, 30.6 Hz), 118.4 (tt, J = 313.9, 45.1 Hz), 128.4, 129.0, 129.5 (t, J = 21.1 Hz), 129.7, 130.3 (2C), 130.4, 134.2, 137.0 (t, J = 8.7 Hz), 138.7; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.18 (t, J = 5.7 Hz, 2F), −106.12 (t, J = 5.7 Hz, 2F); IR (neat) ν 3087, 3058, 3030, 2924, 1638, 1514, 1449, 1227, 1152, 1082, 960, 941, 839, 768 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{13}{}^{79}BrF_4$ $[M]^+$ 372.0137, found 372.0146.

*Methyl 4-(4-Bromo-3,3,4,4-tetrafluoro-1-phenylbut-1-en-2-yl)-phenyl Ketone (**10j**).* Chromatography (silica gel, hexane/ethyl acetate 10:1) afforded **10j** (0.11 g, 66%, E/Z = 94/6) as a white solid: mp 86.0−87.2 °C.

***E*-10j**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 3H), 6.95 (d, J = 7.8 Hz, 2H), 7.14−7.24 (m, 3H), 7.29 (s, 1H), 7.39 (d, J = 7.8 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 114.4 (tt, J = 256.9, 31.0 Hz), 118.0 (tt, J = 357.7, 43.3 Hz), 128.4 (t, J = 21.8 Hz), 128.5, 128.8, 129.3, 130.2, 131.0, 133.5, 137.1, 138.0 (t, J = 8.6 Hz), 138.4, 197.7; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −62.55 (t, J = 5.7 Hz, 2F), −105.98 (t, J = 5.7 Hz, 2F); IR (KBr) ν 3347, 3106, 3057, 3035, 2962, 2921, 2856, 2370, 2294, 1955 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{14}{}^{79}BrF_4O$ $[M + H]^+$ 401.0164, found 401.0160.

Reductive Coupling of $BrCF_2CF_2$-Containing Multisubstituted Alkenes with Various Electrophiles in the Presence of MeLi/LiBr-free. To a solution of **4a** (0.14g, 0.5 mmol) in THF (1.0 mL) was added a benzaldehyde (0.12 mL, 0.1 mmol) at −78 °C. After about 10 min, to this mixture was added dropwise MeLi/LiBr-free (1.12 M, 1.1 mL, 1.2 mmol), and the whole mixture was stirred at that temperature for 2 h. The mixture was quenched with NH_4Cl(aq), and the whole mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, and then filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 5/1) to give the corresponding alcohol **11a** (0.11 g, 0.4 mmol, 72% yield).

*(E)-2,2,3,3-Tetrafluoro-1,5-diphenylpent-4-en-1-ol (**11a**).* Yellow oil: yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (d, J = 3.7 Hz, 1H), 5.16−5.22 (m, 1H), 6.25 (dt, J = 16.1, 12.4 Hz, 1H), 7.09 (dt, J = 16.1, 2.2 Hz, 1H), 7.38−7.45 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.3 (dd, J = 28.2, 23.0 Hz), 115.9 (tt, J = 256.8, 33.3 Hz), 116.6 (tt, J = 250.1, 34.2 Hz), 117.0 (t, J = 23.2 Hz), 127.6, 128.2, 128.5, 128.9, 129.3, 129.7, 134.3, 135.3, 137.6 (t, J = 9.6 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −110.30 (dd, J = 261.3, 12.4 Hz, 1F), −111.19 (dd, J = 261.3, 12.4 Hz, 1F), −120.35 (dm, J = 271.9, 1F), −126.87 (dd, J = 271.9, 16.4 Hz, 1F); IR (neat) ν 3583, 3435, 3066, 3031, 1659, 1496, 1453, 1304, 1207, 1167, 1114, 1071, 974, 763, 718, 691 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{15}F_4O$ $[M + H]^+$ 311.1059, found 311.1056.

*(E)-5,5,6,6-Tetrafluoro-8-phenyloct-7-en-4-ol (**11b**).* Chromatography (silica gel, hexane/ethyl acetate 5/1) afforded **11b** (0.12 g, 85%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 3H), 1.39−1.51 (m, 1H), 1.60−1.84 (m, 3H), 2.33 (d, J = 6.1 Hz, 1H), 4.13 (br s, 1H), 6.34 (dt, J = 16.1, 12.6 Hz, 1H), 7.12 (d, J = 16.1 Hz, 1H), 7.36−7.42 (m, 3H), 7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.6, 31.5, 70.0 (dd, J = 27.8, 24.0 Hz), 116.6 (tt, J = 249.7, 33.7 Hz), 116.7 (tt, J = 255.3, 34.0 Hz), 117.2 (t, J = 23.3 Hz), 127.6, 128.9, 129.7, 134.4, 137.4 (t, J = 9.7 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −111.22 to −111.27 (m, 2H), −122.44 (dd, J = 272.5, 6.1 Hz, 1F), −128.18 (dd, J = 272.5, 16.4 Hz, 1F); IR (neat) ν 3583, 3427, 2965, 2876, 1654, 1446, 1192, 1117, 1069 cm^{-1}; HRMS (FAB+) calcd for $C_{14}H_{16}F_4O$ $[M]^+$ 276.1137, found 276.1142.

*(E)-2,2,3,3-Tetrafluoro-5-(4-methylphenyl)-1-phenylpent-4-en-1-ol (**11c**).* Chromatography (silica gel, hexane/ethyl acetate 5/1) afforded **11c** (0.12 g, 64%) as a yellow solid: mp 78.6−79.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.91 (s, 1H), 5.20 (dd, J = 16.3, 7.8 Hz, 1H), 6.22 (dt, J = 16.1, 12.5 Hz, 1H), 7.09 (d, J = 16.1 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.42−7.52 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 72.3 (dd, J = 28.3, 23.0 Hz), 115.8 (t, J = 23.1 Hz), 115.9 (tt, J = 256.6, 33.2 Hz), 116.7 (tt, J = 250.1, 33.4 Hz), 127.5, 128.2, 128.5, 129.3, 129.6, 131.5, 135.4, 137.5 (t, J = 9.6 Hz), 139.9; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −110.08 (dd, J = 260.8, 12.5 Hz, 1F), −110.90 (dd, J = 260.8, 12.5 Hz, 1F), −120.36 (dm, J = 271.4 Hz, 1F), −126.90 (dd, J = 271.4, 16.3 Hz, 1F); IR (KBr) ν 3358, 3265, 3061, 3033, 2922, 2860, 1955, 1899, 1660, 1608, 1515, 1456 cm^{-1}; HRMS (FAB+) calcd for $C_{18}H_{16}F_4O$ $[M]^+$ 324.1137, found 324.1135.

*(E)-5,5,6,6-Tetrafluoro-8-(4-methylphenyl)oct-7-en-4-ol (**11d**).* Chromatography (silica gel, hexane/ethyl acetate 5/1) afforded **11d** (0.15 g, 83%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, J = 7.2 Hz, 3H), 1.43−1.48 (m, 1H), 1.60−1.79 (m, 3H), 1.99 (d, J = 7.0 Hz, 1H), 2.37 (s, 3H), 4.07−4.11 (m, 1H), 6.25 (dt, J = 16.2, 12.5

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631

Hz, 1H), 7.06 (dt, J = 16.2, 2.4 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 18.6, 21.4, 31.6, 70.0 (dd, J = 27.8, 23.9 Hz), 116.1 (t, J = 23.3 Hz), 116.7 (tt, J = 255.6, 33.9 Hz), 116.8 (tt, J = 249.3, 33.8 Hz), 127.5, 129.6, 131.7, 137.3 (t, J = 9.6 Hz), 139.9; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −111.06 (d, J = 12.5 Hz, 2F), −122.58 (dd, J = 272.52, 7.0 Hz, 1F), −128.33 (dd, J = 272.5, 16.3 Hz, 1F); IR (neat) ν 3584, 3408, 3020, 2964, 2933, 2875, 1659, 1611, 1515, 1459, 1236, 1182, 1082, 974, 799 cm^{-1}; HRMS (FAB+) calcd for $C_{15}H_{18}F_4O$ $[M]^+$ 290.1294, found 290.1299.

(E)-Ethyl 4-(3,3,4,4-Tetrafluoro-5-hydroxy-5-phenylpent-1-en-1-yl)benzoate (11e). Chromatography (silica gel, hexane/ethyl acetate 5/1) afforded **11e** (95 mg, 49%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (t, J = 7.2 Hz, 3H), 3.08 (d, J = 4.7 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 5.19 (m, 1H), 6.30 (dt, J = 16.3, 12.2 Hz, 1H), 7.06 (dt, J = 16.3, 2.2 Hz, 1H), 7.36−7.49 (m, 7H), 8.00 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 61.4, 72.3 (dd, J = 28.3, 23.0 Hz), 115.9 (tt, J = 257.1, 33.6 Hz), 116.3 (tt, J = 250.2, 33.4 Hz), 119.6 (t, J = 23.3 Hz), 127.4, 128.2, 128.5, 129.4, 130.1, 131.2, 135.3, 136.3 (t, J = 9.7 Hz), 138.6, 166.3; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −110.70 (dd, J = 262.5, 12.2 Hz, 1F), −111.85 (dd, J = 262.5, 12.2 Hz, 1F), −120.37 (dm, J = 268.4 Hz, 1F), −126.70 (dd, J = 268.4, 16.5 Hz, 1F); IR (neat) ν 3455, 3058, 2984, 2935, 1703, 1659, 1609, 1571, 1456, 1415, 1370, 1287, 1099, 975 cm^{-1}; HRMS (FAB+) calcd for $C_{20}H_{19}F_4O_3$ $[M + H]^+$ 383.1270, found 383.1267.

(E)-Ethyl 4-(3,3,4,4-Tetrafluoro-5-hydroxyoct-1-en-1-yl)benzoate (11f). Chromatography (silica gel, hexane/ethyl acetate 5/1) afforded **11f** (91 mg, 53%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.0 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 1.39−1.79 (m, 4H), 2.63 (d, J = 4.4 Hz, 1H), 4.08 (br s, 1H), 4.36 (q, J = 7.1 Hz, 2H), 6.40 (dt, J = 16.1, 12.3 Hz, 1H), 7.08 (d, J = 16.1 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 14.3, 18.5, 31.5, 61.3, 69.9 (dd, J = 27.9, 24.0 Hz), 116.3 (tt, J = 249.7, 33.5 Hz), 116.7 (tt, J = 255.7, 23.4 Hz), 119.9 (t, J = 23.4 Hz), 127.4, 130.1, 131.2, 136.1 (t, J = 9.6 Hz), 138.6, 166.3; ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −111.36 (dd, J = 262.4, 12.3 Hz, 1F), −112.15 (dd, J = 262.4, 12.3 Hz, 1F), −122.17 (d, J = 272.3 Hz, 1F), −128.36 (dd, J = 272.3, 16.8 Hz, 1F); IR (neat) ν 3459, 3042, 2964, 2936, 2876, 1933, 1704, 1660, 1610, 1572 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{21}F_4O_3$ $[M + H]^+$ 349.1427, found 349.1427.

2,2,3,3-Tetrafluoro-1,5,5-triphenylpent-4-en-1-ol (11g). Chromatography (silica gel, hexane/ethyl acetate 4/1) afforded **11g** (0.12 g, 61%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (br s, 1H), 5.16 (dd, J = 16.8, 6.6 Hz, 1H), 6.23 (t, J = 14.9 Hz, 1H), 7.24−7.52 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.1 (dd, J = 28.5, 22.8 Hz), 115.5 (t, J = 20.9 Hz), 115.9 (tt, J = 255.6, 33.0 Hz), 116.3 (tt, J = 251.2, 33.0 Hz), 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 129.1, 129.26, 129.33, 135.4, 138.3, 141.3, 151.9 (t, J = 4.4 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −102.72 (dd, J = 269.8, 14.9 Hz, 1F), −103.58 (dd, J = 269.9, 14.9 Hz, 1F), −119.90 (d, J = 271.3, 1F), −127.27 (dd, J = 271.3, 16.8 Hz, 1F); IR (neat) ν 3583, 3436, 3060, 3033, 2926, 1956, 1891, 1812, 1637, 1494, 1456, 1227, 1181, 1146, 1094, 1072 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{18}F_4O$ $[M]^+$ 386.1294, found 386.1301.

2,2,3,3-Tetrafluoro-1,4-diphenylpent-4-en-1-ol (11h). Chromatography (silica gel, hexane/ethyl acetate 5/1) afforded **11h** (1.06 g, 82%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (br s, 1H), 5.15 (dd, J = 17.6, 6.4 Hz, 1H), 5.71 (t, J = 1.4 Hz, 1H), 5.95 (s, 1H), 7.35−7.42 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.1 (dd, J = 28.8, 22.6 Hz), 115.6 (tt, J = 254.9, 35.3 Hz), 116.8 (tt, J = 253.9, 34.6 Hz), 123.8 (t, J = 9.1 Hz), 128.0, 128.1, 128.3, 128.4, 128.7, 129.1, 135.1, 136.1, 140.3 (t, J = 22.0 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −108.25 (d, J = 267.4 Hz, 1F), −109.06 (d, J = 267.4 Hz, 1F), −116.00 (d, J = 278.7 Hz, 1F), −125.58 (dd, J = 278.7, 17.7 Hz, 1F); IR (neat) ν 3435, 1496, 1199, 1114, 1070, 1029, 967, 946, 776, 735, 699 cm^{-1}; HRMS (FAB+) calcd for $C_{17}H_{14}F_4NaO$ $[M + Na]^+$ 333.0878, found 333.0879.

(E)-2,2,3,3-Tetrafluoro-1,4,5-triphenylpent-4-en-1-ol (11i). Chromatography (silica gel, hexane/ethyl acetate 4/1) afforded **11i** (84 mg, 72%) as a white solid: mp 124.7−124.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (br s, 1H), 5.24 (dd, J = 17.4, 6.0 Hz, 1H), 6.98 (d, J = 6.92 Hz, 2H), 7.14−7.22 (m, 4H), 7.32−7.47 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.3 (dd, J = 28.9, 22.7 Hz), 116.1 (tt, J = 257.8, 37.2 Hz), 117.0 (tt, J = 254.5, 34.8 Hz), 119.0, 128.2, 128.35, 128.42, 128.6, 128.7, 129.1, 130.1, 130.6, 131.5 (t, J = 21.4 Hz), 134.1, 134.3, 135.3, 135.5 (t, J = 9.3 Hz); ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$) δ −107.07 (d, J = 261.2 Hz, 1F), −107.98 (d, J = 261.2 Hz, 1F), −115.47 (dm, J = 275.7 Hz, 1F), −124.6 (dm, J = 275.7 Hz, 1F); IR (KBr) ν 3612, 3570, 3087, 3052, 3030, 3010, 2918, 2250, 1959, 1895, 1645, 1496, 1450, 1399, 1333 cm^{-1}; HRMS (FAB+) calcd for $C_{23}H_{18}F_4O$ $[M]^+$ 386.1294, found 386.1292.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02793.

^{1}H and ^{13}C spectra for all of the products and crystal structures PDF)

Crystallographic data (CIF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*T.K.: e-mail, konno@kit.ac.jp; fax, +81-75-724-7504

ORCID

Tsutomu Konno: 0000-0002-5146-9840

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Tosoh F-Tech, Inc., is acknowledged for a generous gift of 4-bromo-3,3,4,4-tetrafluoro-1-butene.

■ REFERENCES

(1) For reviews on the unique characteristics of a fluorine atom, see: (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308−319. (b) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881−1886. (c) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303−319. (d) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992−1020. (e) Kirk, K. *J. Fluorine Chem.* **2006**, *127*, 1013−1029. (f) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3−11. (g) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645−652.

(2) For reviews on the synthetic methods for the preparation of various fluorine-containing molecules, see: (a) Charpentier, J.; Früh, N.; Togni, A. *Chem. Rev.* **2015**, *115*, 650−682. (b) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214−8264. (c) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455−529 and references cited therein.

(3) (a) Yamada, S.; Higashi, M.; Konno, T.; Ishihara, T. *Eur. J. Org. Chem.* **2016**, *2016*, 4561−4568. (b) Yamada, S.; Hondo, K.; Konno, T.; Ishihara, T. *RSC Adv.* **2016**, *6*, 28458−28469. (c) Nihei, T.; Hoshino, T.; Konno, T. *Org. Lett.* **2014**, *16*, 4170. (d) Konno, T.; Kishi, M.; Ishihara, T.; Yamada, S. *Tetrahedron* **2014**, *70*, 2455−2463. (e) Konno, T.; Kinugawa, R.; Ishiihara, T.; Yamada, S. *Org. Biomol. Chem.* **2014**, *12*, 1611−1617. (f) Nihei, T.; Yokotani, S.; Ishihara, T.; Konno, T. *Chem. Commun.* **2014**, *50*, 1543−1545 and references cited therein.

(4) For papers for compounds having a perfluoroalkyl fragment, except for a tetrafluoroethylene group, see: (a) Kaplan, P. T.; Vicic, D. A. *Org. Lett.* **2016**, *18*, 884−886. (b) Kaplan, P. T.; Chen, B.; Vicic, D. A. *J. Fluorine Chem.* **2014**, *168*, 158−162. (c) Kaplan, P. T.; Xu, L.; Chen, B.; McGarry, K. R.; Yu, S.; Wang, H.; Vicic, D. A. *Organometallics* **2013**, *32*, 7552−7558. (d) Kim, H. W.; Rossi, P.; Schoemaker, R. K.; DiMagno, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 9082−9083. (e) Biffinger, J. C.; Kim, H. W.; DiMagno, S. G. *ChemBioChem* **2004**, *5*, 622−627.

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631

(5) For our studies on the preparation of compounds having a tetrafluoroethylene fragment, see: (a) Watanabe, Y.; Konno, T. *J. Fluorine Chem.* **2015**, *174*, 102−107. (b) Konno, T.; Hoshino, T.; Kida, T.; Takano, S.; Ishihara, T. *J. Fluorine Chem.* **2013**, *152*, 106−113. (c) Konno, T.; Takano, S.; Takahashi, Y.; Konishi, H.; Tanaka, Y.; Ishihara, T. *Synthesis* **2011**, *2011*, 33−44.

(6) (a) van Straaten, K. E.; Kuttiyatveetil, J. R. A.; Sevrain, C. M.; Villaume, S. A.; Jiménez-Barbero, J.; Linclau, B.; Vincent, S. P.; Sanders, D. A. *J. Am. Chem. Soc.* **2015**, *137*, 1230−1244. (b) Ioannou, A.; Cini, E.; Timofte, R. S.; Flitsch, S. L.; Turner, N. J.; Linclau, B. *Chem. Commun.* **2011**, *47*, 11228−11230. (c) Linclau, B.; Boydell, A. J.; Timofte, R. S.; Brown, K. J.; Vinader, V.; Weymouth-Wilson, A. C. *Org. Biomol. Chem.* **2009**, *7*, 803−814. (d) Timofte, R.; Linclau, B. *Org. Lett.* **2008**, *10*, 3673−3676. (e) Boydell, A. J.; Vinader, V.; Linclau, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 5677−5679.

(7) (a) Konno, T.; Ishihara, T.; Asai, T.; Ihara, S. PCT Int. Appl. WO2014125924 A1. (b) Konno, T.; Ishihara, T.; Asai, T.; Ihara, S. PCT Int. Appl. WO2014010665 A1. (c) Yamada, S.; Hashishita, S.; Asai, T.; Ishihara, T.; Konno, T. *Org. Biomol. Chem.* **2017**, DOI: 10.1039/C6OB02431A.

(8) (a) Budinská, A.; Václavík, J.; Matousek, V.; Beier, P. *Org. Lett.* **2016**, *18*, 5844. (b) Matousek, V.; Václavík, J.; Hájek, P.; Charpentier, J.; Blastik, Z. E.; Pietrasiak, E.; Budinská, A.; Togni, A.; Beier, P. *Chem. - Eur. J.* **2016**, *22*, 417−424. (c) O'duill, M.; Dubost, E.; Pfeifer, L.; Gouverneur, V. *Org. Lett.* **2015**, *17*, 3466−3469. (d) Ohashi, M.; Shirataki, H.; Kikushima, K.; Ogoshi, S. *J. Am. Chem. Soc.* **2015**, *137*, 6496−6499. (e) Saijo, H.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2014**, *136*, 15158−15161. (f) Chernykh, Y.; Hlat-Glembová, K.; Klepetárová, B.; Beier, P. *Eur. J. Org. Chem.* **2011**, *2011*, 4528−4531. (g) Bonnac, L.; Lee, S. E.; Giuffredi, G. T.; Elphick, L. M.; Anderson, A. A.; Child, E. S.; Mann, D. J.; Gouverneur, V. *Org. Biomol. Chem.* **2010**, *8*, 1445−1454.

(9) (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2964. (b) Beletskaya, I.; Cheprakav, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066. (c) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. (d) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581.

(10) (a) Darses, S.; Pucheault, M.; Genêt, J.-P. *Eur. J. Org. Chem.* **2001**, *2001*, 1121−1128. For other Heck reactions of fluorinated alkenes, see. (b) Konno, T.; Yamada, S.; Tani, A.; Nishida, M.; Miyabe, T.; Ishihara, T. *J. Fluorine Chem.* **2009**, *130*, 913−921. (c) Konno, T.; Yamada, S.; Tani, A.; Miyabe, T.; Ishihara, T. *Synlett* **2006**, *2006*, 3025−3028.

(11) (a) Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405−3406. (b) Darses, S.; Jeffery, T.; Brayer, J.-L.; Demoute, J.-P.; Genêt, J.-P. *Bull. Soc. Chim. Fr.* **1996**, *133*, 1095−1102. (c) Doyle, M. P.; Bryker, W. J. *J. Org. Chem.* **1979**, *44*, 1572−1574. (d) Suschitzky, H. *Adv. Fluorine Chem.* **1965**, *4*, 1−30. (e) Roe, A. *Organic Syntheses*; Wiley: New York, 1949; Collect. Vol. *4*, pp 193−228

(12) In all cases, the coupling constants between the vicinal olefinic protons in **4** are ca. 16 Hz, strongly indicating that the Heck adducts 4 have an *E* configuration at the olefinic bond.

(13) It has been reported that $Pd(OAc)_2$ reacts with MeOH to afford Pd(0), formaldehyde, and acetic acid: Sajiki, H.; Ikawa, T.; Yamada, H.; Tsubouchi, K.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 171−174.

(14) A similar reaction mechanism has been reported. See: Limberger, J.; Poersch, S.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2011**, *22*, 1389−1394.

(15) In order to prevent the isomerization from proceeding, various bases, such as Et_3N, CH_3CO_2K, CH_3CO_2Na, Na_3PO_4, $NaHCO_3$, K_2CO_3, and *t*-BuOK, were throughly examined, but satisfactory results could not be obtained.

(16) We also performed a reaction in which **5b** with an *E*/*Z* ratio of 28/72 was treated with 3.3 equiv of benzenediazonium tetrafluoroborate in the presence of 10 mol % of $[Pd_2(dba)\cdot CHCl_3]$ and 40 mol % of P(*o*-Tol)$_3$ in MeOH at 40 °C for 24 h. As a result, the starting **5b** was recovered quantitatively without any change in the *E*/*Z* ratio of **5b**. This strongly indicates that **Int-D** is involved in the isomerization.

(17) Baum, K.; Bedford, C. D.; Hunad, R. J. *J. Org. Chem.* **1982**, *47*, 2251−2257.

(18) Götzö, S. P.; Seebach, D. *Chimia* **1996**, *50*, 20−23.

(19) (a) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062−5085. (b) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461−1473. (c) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544−4568. (d) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (e) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866−867. (f) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437−3440.

DOI: 10.1021/acs.joc.6b02793
J. Org. Chem. 2017, 82, 1618−1631