Journal of Fluorine Chemistry 135 (2012) 144–154

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Preparation of *p*-substituted tetrafluoropyridyl derivatives *via* the tetrafluoropyridylcopper reagent☆

Ba Van Nguyen, Donald J. Burton *

Department of Chemistry, The University of Iowa, Iowa City, IA 52242, USA

ARTICLE INFO

Article history:
Received 5 August 2011
Received in revised form 8 September 2011
Accepted 1 October 2011
Available online 6 October 2011

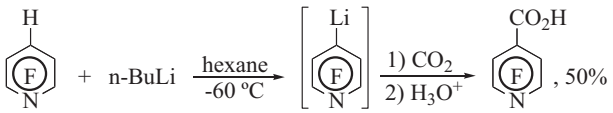
Keywords:
4-Tetrafluoropyridylcopper reagent
4-Iodotetrafluoropyridine
Organometallic reagents
Coupling reactions
4-Tetrafluoropridyl derivatives
Pd(0) catalyzed reactions

ABSTRACT

A new and improved preparation of 4-iodo-2,3,5,6-tetrafluoropyridine from pentafluoropyridine is described. This iodopyridine is utilized for the *in situ* preparation of the 4-tetrafluoropyridylcopper reagent, **1**, *via* two methods. The first method involves metathesis of the 4-tetrafluoropyridylcadmium reagent with Cu(I)Br at room temperature. The requisite cadmium reagent was readily prepared *in situ via* reaction between 4-iodotetrafluoropyridine with acid-washed cadmium powder in DMF at room temperature. The second method involves the *in situ* reaction of 4-tetrafluoropyridyltributylphosphonium tetrafluoroborate with Na_2CO_3 and Cu(I)Br in DMF at room temperature. **1** readily undergoes reaction with allylic halides, vinyl iodides, aryl halides, acid chlorides and acetylenic iodides at room temperature to stereospecifically afford the corresponding 4-tetrafluoropyridyl derivatives. An alternative route to the alkyne derivatives was developed *via* the Pd(0) catalyzed reaction of 4-iodotetrafluoropyridine with 1-alkynes.

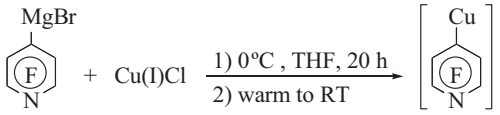
1. Introduction

The chemistry of pentafluoropyridine has been investigated since the early 1960s. The majority of reactions of pentafluoropyridine involve the replacement of the 4-fluorine atom by nucleophilic reagents [1]. Nucleophilic reactions are useful for the introduction of certain functional groups into the perfluoropyridine nucleus; however, this methodology does have some disadvantages, in that only nucleophiles can be introduced and the nucleophilic substitution may give more than one product. In addition, nucleophilic substitution is not readily applicable to the preparation of functionalized pyridines. Alternatively, organometallic reagents, such as 4-tetrafluoropyridyllithium or magnesium reagents have been utilized to prepare functionalized 4-tetrafluoropyridyl derivatives, Eq. (1) [2].



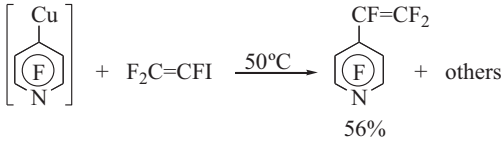
(1)

The corresponding Grignard reagent is somewhat more stable than the lithium reagent and has also been utilized to prepare the 4-tetrafluoropridylcopper reagent, Eq. (2) [3].



(2)

The pyridylcopper reagent was coupled with iodotrifluoroethene to give (4-tetrafluoropyridyl)trifluoroethene, Eq. (3) [4]. By-products included 2,3,5,6-tetrafluoropyridine, 4-iodo-tetrafluoropyridine and bis (4,4′-tetrafluoropyridine). The disadvantages of this approach are low temperature preparation of the organolithium or Grignard reagent is required and that the 4-bromo- or 4-iodotetrafluoropyridine precursors to the organometallic intermediates are isolated in moderate yields from multistep syntheses.



(3)

2. Results and discussion

2.1. Preparation of 4-iodotetrafluoropyridine

4-Iodotetrafluoropyridine has been prepared by a one-step reaction from pentafluoropyridine *via* the high temperature reaction of the pyridine with iodide ion as the nucleophile,

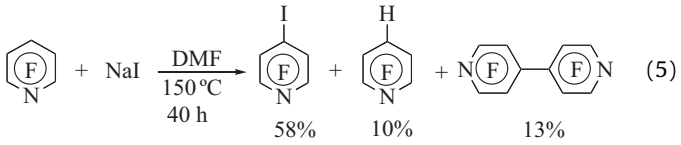
☆ Presented in part at the 20th Winter Fluorine Conference, St. Petersburg Beach, FL; January 2011, Abstract #35.

* Corresponding author. Tel.: +1 319 335 1363; fax: +1 319 335 1270.
E-mail addresses: donald-burton@uiowa.edu, mburton105@gmail.com (D.J. Burton).

0022-1139/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2011.10.001

Eq. (4) [5]. Efforts to improve the conversion (longer reaction times) made little difference in the yield of the 4-iodopyridine but generated additional by-products [5], Eq. (5).

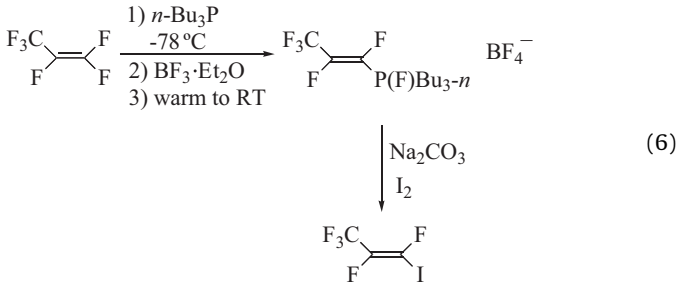
(4)



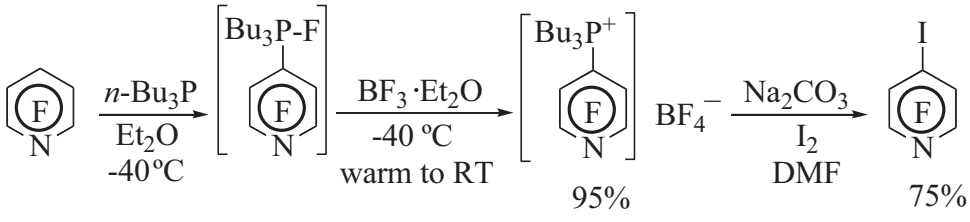
(5)

The authors demonstrated that prolonged reaction of the 4-iodotetrafluoropyridine with iodide ion at 150 °C promoted attack by the iodide ion on the iodopyridine to generate the tetrafluoropyridyl anion – which accounted for the by-products at long reaction times.

Thus, our first objective was to identify an improved method to this key precursor. We have reported a general route to (*Z*)-1-iodoperfluoroolefins *via* the reaction of the perfluoroolefin with *n*-tributylphosphine at low temperatures. The resultant vinyl (*Z*)-phosphorane is subsequently reacted *in situ* with boron trifluoride etherate to afford the (*Z*)-perfluoroalkenyltributylphosphonium tetrafluoroborate. Subsequent *in situ* cleavage of the tetrafluoroborate salt with either Na_2CO_3/I_2 or KF/I_2 affords stereospecifically the (*Z*)-1-iodoperfluoroalkene, illustrated in Eq. (6) with perfluoropropene [6]. Since the sp^2 carbon of the perfluoroolefin is readily attacked by the nucleophilic tertiary phosphine, we anticipated that the highly reactive pentafluoropyridine would behave similarly. To our delight, we found that pentafluoropyridine reacted rapidly with *n*-tributylphosphine at −45 to −35 °C in dry diethyl ether to generate the 4-pyridylphosphorane. Subsequent addition of $BF_3{\cdot}Et_2O$ to the cold phosphorane solution provided the corresponding phosphonium tetrafluoroborate in 95% yield. Subsequent reaction of the tetrafluoroborate salt with Na_2CO_3/I_2 in dry DMF gave (after flash distillation) a ^{19}F NMR yield of 92% 4-iodotetrafluoropyridine in DMF. Subsequent workup provided a 75% isolated yield of the 4-iodotetrafluoropyridine as a white solid, mp 49–51 °C (reported mp 47–48 °C [5]), Eq. (7).



(6)

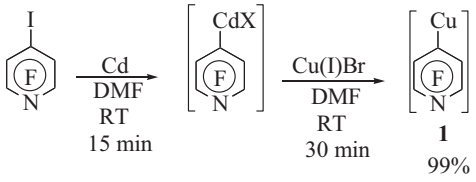


(7)

Although 4-iodotetrafluoropyridine is easily obtained from the purified, isolated phosphonium salt intermediate, the entire transformation (Eq. (7)) can be carried out as a one pot synthesis.

2.2. In situ preparation of the 4-tetrafluoropyridylcopper reagent

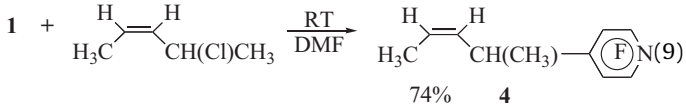
We have recently described the *in situ* preparation of perfluoroarylcadmium reagents *via* direct reaction of a perfluoroaryl halide with cadmium [7–10]. Similarly, 4-tetrafluoropryidylcadmium formation readily occurs when 4-iodotetrafluoropyridine is reacted with acid-washed cadmium powder in DMF at RT. Subsequent *in situ* exchange of the arylcadmium reagent with Cu(I)Br provides the corresponding 4-tetrafluoropridylcopper reagent, **1**, Eq. (8) [11]. The cadmium reagent has been previously prepared *via* pyrolysis of the cadmium-4-tetrafluoro-pyridylcarboxylate [12]. The thermal stability of a solution of **1** is excellent. When **1** was stored in a degassed, sealed tube at RT for 48 h, no decomposition was observed. When a solution of **1** was heated at 90 °C for 3 h, the color of the solution changes slightly from brown to dark brown, but the ^{19}F NMR spectrum of the reagent exhibits no significant changes.



(8)

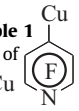
2.3. Reaction of 1 with allylic halides and propargyl tosylate

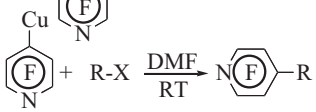
1 reacts smoothly with primary allylic halides to form the corresponding coupling product in high yields at RT (Table 1). Secondary allylic halides, such as (*Z*)-4-chloro-2-pentene, also stereospecifically give a good yield (74%) of the coupled product, **4**, Eq. (9).

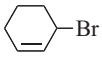
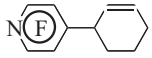
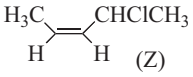
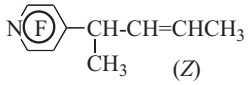
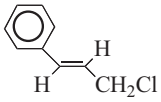
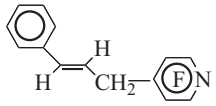
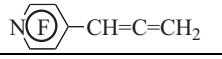


(9)

In all cases, no evidence of substitution at the γ-carbon *via* an SN'_2 mechanism was observed. In contrast to CF_2HCu [13], **1** does not attack the γ-carbon of these allylic halides to form γ-substituted products. In the case of propargyl tosylate, **1** gave only the 2,3,5,6-tetrafluoropyridyl substituted allene, **6,** Eq. (10). The allene product was formed by attack of **1** at the γ-carbon of propargyl tosylate *via* an SN'_2 mechanism, similar to other

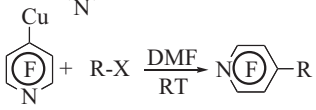
Table 1
Rx. of  with allylic halides and propargyl tosylate.

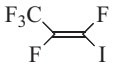
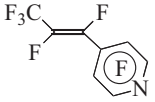
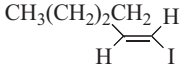
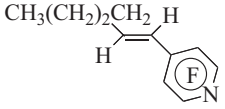
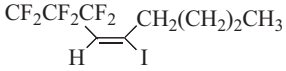
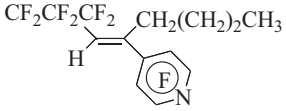
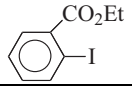
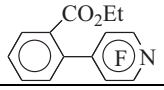


Compd. #	R–X	Pdt.	%Yield[a]
2	$(CH_3)_2C{=}CHCH_2Br$		61
3			82
4			74
5			86
6	$HC{\equiv}CCH_2OTs$		63

[a] Isolated yields.

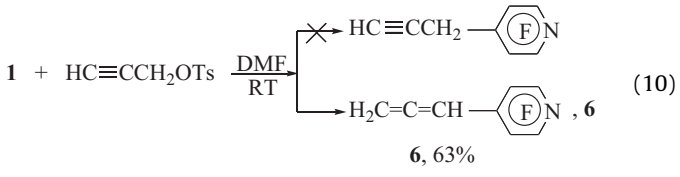
Table 2
Rx.  of with vinyl iodides and aryl iodides.



Compd. #	R–X	Pdt	% Yield[a]
7	R-X	Pdt	85
			
8			85
9			91
10			80

[a] Isolated yields.

reactions previously reported with propargyl tosylate and fluorinated copper reagents [14].



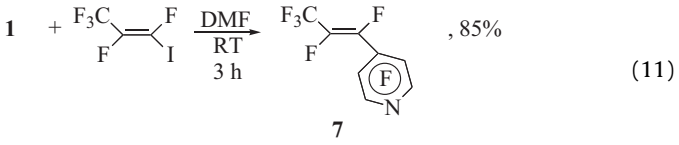
(10)

6, 63%

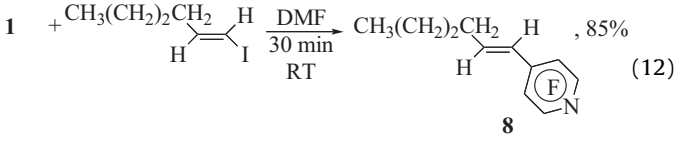
2.4. Reaction of 1 with vinyl iodides and aryl iodide

Coupling of **1** with internal and terminal vinyl iodides occurs at RT to afford the expected coupled products with perfluorinated, non-fluorinated or partially fluorinated vinyl iodides (Table 2). In all cases, the stereochemistry of the starting vinyl iodide is retained in the products and there is no detectable metal-halogen exchange by ^{19}F NMR analysis of the reaction mixture. The stereochemistry of the (*Z*)-and (*E*)-isomers could be verified by the NMR coupling constants of the vinyl fluorines of the products. For example, **1**, reacts with (*Z*)-1-iodopentafluoropropene at RT under a nitrogen

atmosphere to give an 85% isolated yield of (*E*)-1-(2,3,5,6-tetrafluoropyridyl)pentafluoropropene, **7**, in which the coupling constant between the two vinylic fluorines is 140.0 Hz. In the case of a hydrocarbon substrate, **1** reacts with (*E*)-1-iodo-1-hexene to form (*E*)-1-(2,3,5,6-tetrafluoropyridyl)-1-hexene, **8**, in 85% yield. The coupling constant of the two vinylic hydrogens is 16.3 Hz, cf. Eqs. (11) and (12). **1** also reacts smoothly with a functionalized aryl iodide to give the expected tetrafluoropyridyl coupled product, **10**.



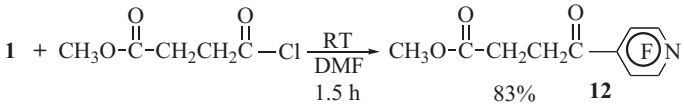
(11)



(12)

2.5. Reaction of 1 with acyl halides

The coupling of **1** with acyl halides occurs smoothly at RT to give a variety of ketones in 72–93% isolated yields (Table 3). For example, **1** reacts with 3-carbomethoxypropionyl chloride at RT to give methyl-4-(2,3,5,6-tetrafluoropyridyl)-4-oxo-butanoate, **12** in 83% yield, Eq. (13). Both aryl and alkyl acyl halides react readily.



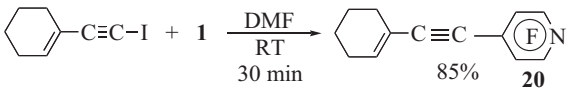
(13)

Interestingly, the reaction of 4- or 2-bromobenzoyl chloride gave only the ketone products, **14** and **15**, leaving the aryl bromine bond intact, Eq. (14).

(14)

2.6. Reaction of 1 with 1-iodoalkynes

1-Iodoalkynes react exothermically with **1** at RT to give the corresponding coupled products in high yields (Table 4). In most cases, the reaction is complete in less than 30 min with the substituent groups on the alkynyl iodides showing little effect on the rate of the coupling reaction. In all cases, there is no evidence of exchange between the alkyne and the copper reagent or other fluorine-containing products in these reactions that could be detected by ^{19}F NMR analysis of the reaction mixture. Both alkyl, aryl and functionalized 1-iodoalkynes reacted readily, Eq. (15).

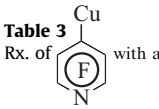


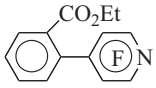
(15)

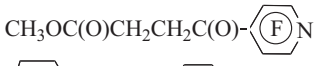
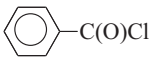
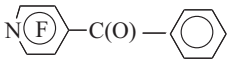
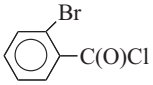
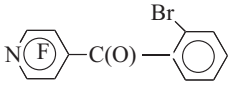
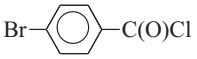
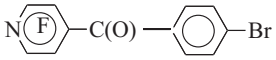
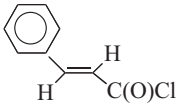
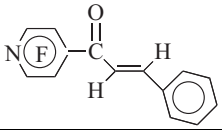
2.7. Pd catalyzed reaction of 4-iodotetrafluoropyridine with 1-alkynes

The coupling reaction between 4-tetrafluoropyridylcopper and 1-iodoalkynes is an excellent reaction. However, its synthetic utility is limited, since 1-iodoalkynes are not commercially available, and hydroxyl or amino substituted 1-iodoalkynes are difficult to prepare. The key to overcoming this problem is to utilize methodology which directly introduces the alkynyl group to 4-iodotetrafluoropyridine utilizing terminal alkynes [15–18], thus avoiding the necessity of the 1-iodoalkyne.

Although DMF is generally a convenient solvent for orgnocopper chemistry, we found that it hindered formation of this organocopper complex under Pd-catalyzed conditions. 4-Iodotetrafluoropyridine did not couple to terminal alkynes in the

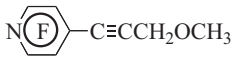
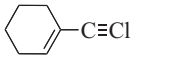
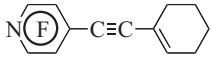
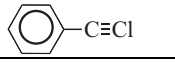
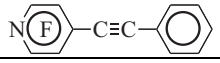
Table 3
Rx. of  with acid chlorides.



Compd. #	RC(O)Cl	Pdt.	% Yield[a]
11	$CH_3CH_2C(O)Cl$		77
12	$CH_3OC(O)CH_2CH_2C(O)Cl$		83
13			78
14			85
15			72
16			93

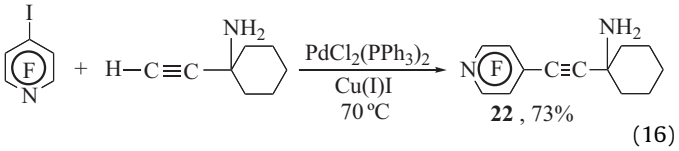
[a] Isolated yields.

Table 4
Rx. of  with acetylenic iodides.

Compd. #	IC≡CR	Pdt.	%Yield[a]
17	$CH_3(CH_2)_2CH_2C{\equiv}Cl$		87
18	$CH_3OCH_2C{\equiv}Cl$		82
19	$CH_3CH(OEt)OCH_2C{\equiv}Cl$		71
20			85
21			91

[a] Isolated yields.

presence of DMF, triethylamine, Cu(I)I salts, and $Pd(PPh_3)_2Cl_2$. However, in the absence of DMF, the coupling reaction proceeded smoothly (Table 5). An advantage of this alternative methodology is that a variety of functionalized alkynes can be employed. For example, 4-iodotetrafluoropyridine reacts with 1-ethynylcyclohexylamine in Et_3N, catalyzed by Pd(0) at 70 °C to afford 73% of (2,3,5,6-tetrafluoropyridyl) (1-amino-cyclohexyl)-ethyne, **22**, Eq. (16). Similarly, the corresponding hydroxyl derivative provided the hydroxyl substituted 4-tetrafluoropyridyl derivative, **23**. Interestingly, water and methanol can be tolerated under these reaction conditions. For example, when (*Z*)-1-methoxy-1-butene-3-yne, commercially available as 50 weight% solution of methanol–water, 4–1, was utilized as a substrate, the corresponding (*Z*)-1-methoxy-4-(2,3,5,6-tetrafluoropyridyl)-1-butene-3-ynl, **25**, was isolated in 35% yield.

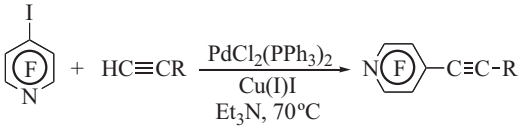


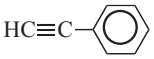
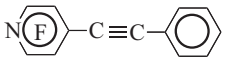
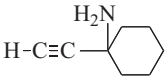
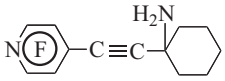
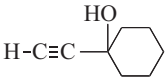
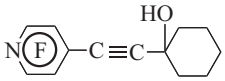
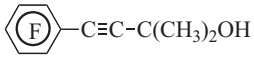
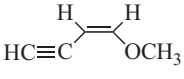
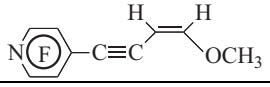
(16)

2.8. In situ formation of the 4-tetraflluoropyridylcopper reagent directly from 4-tetrafluoropyridyltributylphosphonium tetrafluoroborate

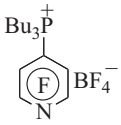
When 4-tetrafluoropyridyltributylphosphonium tetrafluoroborate was treated with Na_2CO_3/I_2, 4-iodotetrafluoropyridine was formed in good yield (cf. Eq. (7)). We speculated that sodium carbonate assisted formation of the 4-tetrafluoropyridyl anion, which was subsequently trapped by I_2. Thus, we rationalized that the phosphonium salt, when treated with Na_2CO_3, would generate the 4-tetrafluoropyridyl anion which could also be trapped *in situ* with a copper(I) salt, such as Cu(I)Br. Thus, we treated the phosphonium tetrafluoborate salt in DMF with Na_2CO_3/Cu(I)/Br at RT and found that the 4-tetrafluoropyridylcopper reagent was indeed *in situ* formed. Subsequent treatment of this solution with several coupling partners, produced the 4-tetrafluoropyridyl derivatives in yields similar to the copper reagent generated from the corresponding cadmium reagent, cf. Table 6. Allylic halides and acid chlorides worked well. In only one case did we observe a distinct difference in reactivity. When

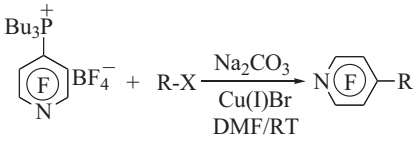
Table 5
Reaction of 4-iodotetrafluoropyridine with terminal alkynes catalyzed by Pd.

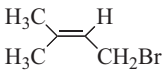
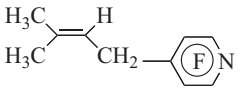
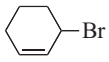
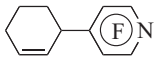
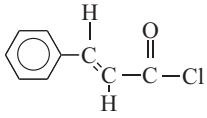
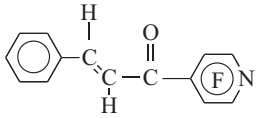
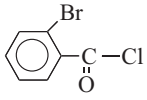
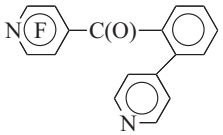
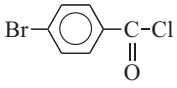
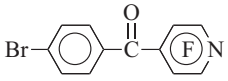


Compd. #	HC≡CR	Pdt.	%Yield[a]
21			88
22			73
23			71
24	$HC{\equiv}C{-}C(CH_3)_2OH$		92
25			35

[a] Isolated yields.

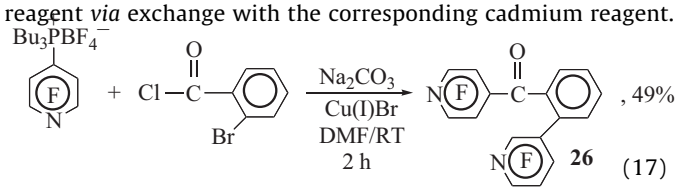
Table 6
Rx. of  with Na_2CO_3/Cu(I)Br + functional derivatives.



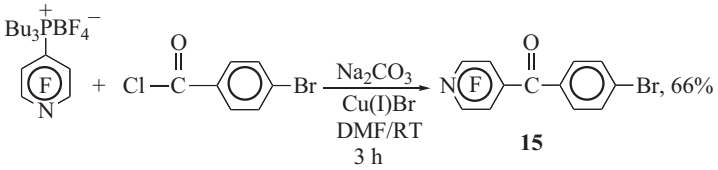
Compd. #	R–X	Pdt.	% Yield[a]
2			64
3			69
16			78
26			49
15			66

[a] Isolated yields.

2-bromobenzoyl chloride was reacted with the copper reagent, formed from the 4-tetrafluoropyridyltributylphosphonium salt, both the acyl halide functionality and the 2-bromoaryl substituent coupled with the copper reagent, Eq. (17). The 4-bromo analog gave only coupling with the acyl function, Eq. (18). Additional experiments are required to determine why the activated 2-bromo substituent couples under these conditions, but not under conditions used with the preparation of the copper reagent *via* exchange with the corresponding cadmium reagent.



, 49% (17)



(18)

2.9. Mechanism of formation of the 4-tetrafluoropyridylcopper reagent and 4-iodo-tetrafluoropyridine from 4-tetrafluoropyridyl tributylphosphonium tetrafluoroborate, Scheme 1

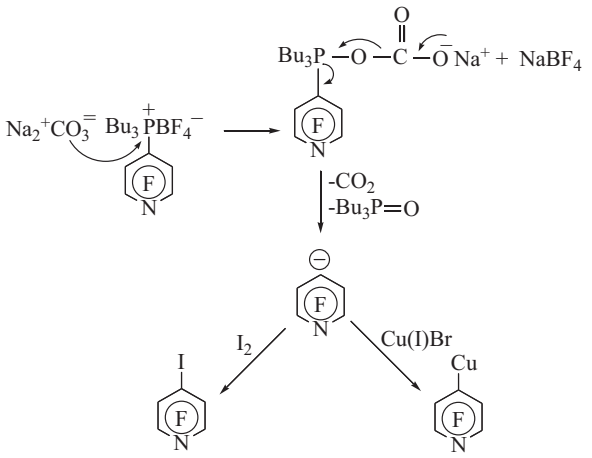
Attack by carbonate on the phosphonium center produces an intermediate that collapses with loss of CO_2 and $Bu_3P{=}O$ to produce the 4-tetrafluoropyridyl anion. If I_2 is utilized as a partner in the Na_2CO_3 reaction, the 4-iodotetrafluoropyridine is formed. If Cu(I)Br is employed as the partner, the anion is trapped by the Cu(I) salt to afford the 4-tetrafluoropyridylcopper reagent. Supporting evidence for this proposed mechanism is as follows: (1) if moisture is present, 4-hydrotetrafluoropyridine is formed as a by-product; (2) if benzaldehyde is used as a partner with Na_2CO_3, a 30% yield of the addition product of the anion to benzaldehyde was isolated.

3. Experimental

3.1. General experimental procedures

All reactions were monitored by ^{19}F NMR analysis of the reaction mixtures on a JEOL FX90Q spectrometer. The ^{1}H, ^{19}F, ^{13}C NMR spectra of the final products were obtained on a Bruker AC-300 spectrometer ($CDCl_3$, $CFCl_3$ or TMS internal references).

FTIR was recorded on a Mattson Cygnes 100 spectrometer as CCl_4 solutions in a 0.1 cm path length cell. Low-resolution mass spectra were obtained on a TRIO-GC–MS and high resolution mass spectra were obtained on a VG Analytical H-250J at 70 eV by the University of Iowa Mass Spectrometry personnel. GLPC analysis was recorded on a Hewlett Packard 5890A gas chromatograph with an OV-101 column and thermal conductivity detector. Melting points were obtained on a Thomas Hoover Capillary melting point apparatus in open-ended capillaries and are uncorrected. All starting materials were obtained from commercial sources and



Scheme 1. Mechanism of cleavage of phosphonium salt with Na_2CO_3.

used directly or by methods previously developed in this laboratory.

3.2. Preparation of 4-(2,3,5,6-tetrafluoropyridyl)tributylphosphonium tetrafluoroborate

A dry, 1 l three-necked flask was equipped with a mechanical stirrer, a pressure-equalized addition funnel, and a low temperature thermometer. The flask was charged with 300 mL of anhydrous diethyl ether and 25.0 g (148 mmol) of pentafluoropyridine. The resultant solution was stirred under a nitrogen atmosphere and cooled to −40 °C in an isopropanol/dry ice bath. *n*-Tributylphosphine (30.0 g, 149 mmol) was added dropwise to the solution *via* the pressure-equalized addition funnel over 2 h at −45 to −35 °C; then 21.0 g (149 mmol) of $BF_3{\cdot}OEt_2$ was added dropwise *via* syringe. The reaction mixture was stirred and warmed to RT. At this point, a white solid deposited on the flask wall. The solvent was removed *via* syringe and the solid was washed with 3× 100 mL of anhydrous diethyl ether under a N_2 atmosphere. The white solid was dried under vacuum for 15 min to give 61.8 g (95%) of 4-(2,3,5,6-tetrafluoropryidyl)tributylphosphonium tetrafluoroborate. ^{19}F NMR: δ −86.6 (m, 2F), −131.1 (m, 2F), −151.8 (s, 4F); ^{1}H NMR: δ 2.7 (m, 6H), 1.6 m (12H), 1.0 (t, $^3J_{HH}$ = 7.1 Hz, 9H); ^{13}C NMR: δ 144.7 (dm, $^1J_{CF}$ = 251.3 Hz), 143.1 (dm, $^1J_{CF}$ = 265.1 Hz), 113.6 (dt, $^1J_{CP}$ = 64.2 Hz, $^2J_{CF}$ = 17.1 Hz), 20.2 (d, $^1J_{CP}$ = 44.7 Hz), 13.1 (s) 23.8 (s), 23.6 (s); ^{31}P NMR: δ 38.0 (m).

3.3. Preparation of 4-iodo-2,3.,5,6-tetrafluoropyridine

The flask containing the phosphonium tetrafluoroborate was re-pressurized with N_2. Then, 250 mL of dry DMF, 94.0 g (370 mmol) I_2, and 39.3 g (370 mmol) of Na_2CO_3 were added under a nitrogen atmosphere. The reaction mixture was stirred at RT for 2 h; then flash distilled to give a mixture of DMF and product. This mixture was poured into a sodium bisulfite solution. The lower layer was separated, diluted with 200 mL Et_2O, and washed with 4× 300 mL H_2O. The organic layer was separated and dried over anhydrous $MgSO_4$. The drying agent was removed by gravity filtration and the product concentrated *via* rotary evaporation. The last traces of solvent were removed under vacuum at 0 °C to give 30.8 g (75%) of a white solid, mp 49–51 °C, 4-iodo-2,3,5,6-tetrafluoropyridine. ^{19}F NMR: δ −89.9 m (2F), −123.1 (m, 2F). ^{13}C NMR: δ 143.7 (dm, $^1J_{CF}$ = 257.4 Hz), 142.8 (dm, $^1J_{CF}$ = 199.0 Hz), 88.7 (t, $^2J_{CF}$ = 26.1 Hz). FTIR (CCl_4, cm^{-1}): 1612 (m), 1457 (s), 1442 (s), 1223 (m), 944 (m), 834 (m). GC–MS, *m*/*z* (relative intensity): 277 (M^+, 100), 150 (40), 100 (45). HRMS calc'd. for C_5F_4NI 276.9012, obsv'd. 276.9004.

3.4. Preparation of 4-(2,3,5,6-tetrafluoropyridyl)cadmium reagent

A dry, two-necked, 50 mL round-bottomed flask equipped with a nitrogen inlet, a Teflon coated stir-bar, and septum port was charged with 5.0 g (18.0 mmol) of 4-iodo-2,3,5,6-tetrafluoropyridine and 2.2 g (20.0 mmol) of acid-washed cadmium powder in 20 mL of dry DMF. The reaction was stirred under a nitrogen atmosphere at room temperature. After stirring for 15 min, the 4-iodo-2,3,5,6-tetrafluoropyridine was completely consumed as determined by ^{19}F NMR analysis, ^{19}F NMR ($CFCl_3$, DMF) δ −98.0 ppm (m, 2F), −118.0 ppm (m, 2F).

3.5. Preparation of 4-(2,3,5,6-tetrafluoropyridyl)copper reagent, 1

A dry, two-necked, 50 mL round-bottomed flask equipped with an nitrogen inlet, a Teflon coated stir-bar, and septum port was charged with 2.9 g (20.0 mmol) of Cu(I)Br. The cadmium reagent described above was added to the flask *via* syringe. The reaction mixture was stirred under a nitrogen atmosphere at room temperature. After stirring for 30 min, the cadmium reagent was completely consumed as determined by ^{19}F NMR analysis, ^{19}F NMR ($CFCl_3$, DMF) −99.3 ppm (m, 2F), −117.4 ppm (m, 2F).

3.6. Preparation of (E)-1-phenyl-3-(2,3,5,6-tetrafluoropyridyl)-1-propene, 5

In a typical experimental procedure, a dry, two-necked, 50 mL round-bottomed flask equipped with a nitrogen inlet, septum port, and a Teflon coated stir-bar was charged with 5 mL of dry DMF and 0.76 g (5.0 mmol) of (*E*)-cinnamyl chloride. The solution was stirred under an argon atmosphere at room temperature, then a solution of **1** (5.0 mmol) was added dropwise *via* syringe. After stirring at room temperature for 1.5 h, the copper reagent had been completely consumed as determined by ^{19}F NMR analysis. The mixture was poured into 200 mL of water and extracted with 3× 100 mL of CH_2Cl_2. The organic layer was separated, washed with 3× 100 mL of water, dried over anhydrous $MgSO_4$, gravity filtered, then concentrated using a rotary evaporator. The crude product was introduced onto a silica-gel column, 3.5 cm o.d. × 20.0 cm long (Baker, 40 μm), and eluted with hexane. The elute containing the product was collected and the solvent was removed by rotary evaporation followed by evaporation under vacuum to give 1.15 g (86%) yield of (*E*)-1-phenyl-3-(2,3,5,6-tetrafluoropyridyl)-1-propene as a solid, mp: 92–94 °C. ^{19}F NMR: δ −91.9 (m, 2F), −145.7 (m, 2F); ^{1}H NMR: δ 3.6 (dm, $^3J_{HH}$ = 6.9 Hz, 2H), 6.2 (dt, $^3J_{HH}$ = 15.6 Hz, $^3J_{HH}$ = 6.9 Hz, 1H), 6.5 (d, $^3J_{HH}$ = 15.7 Hz, 1H), 7.3 (m, 5H). ^{13}C NMR: δ 143.4 (dtm, $^1J_{CF}$ = 244.1 Hz, $^2J_{CF}$ = 16.6 Hz), 140.4 (dm, $^1J_{CF}$ = 256.3 Hz), 132.9 (tm, $^2J_{CF}$ = 20.0 Hz), 136.3 (s), 133.8 (s), 128.6 (s), 127.9 (s), 126.3 (s), 122.2 (s), 27.7 (s). FTIR: (CCl_4, cm^{-1}) 1644.8 (m), 1469.6 (s), 1412.6 (m), 1253.4 (m), 964.4 (m). GC–MS: *m*/*z* (relative intensity) 268 (M^++1, 15.1), 267 (M^+, 100.0), 266 (38.5), 247 (29.0), 117 (27.4), 91 (53.2), 77 (19.1). HRMS: calc'd. for $C_{14}F_4H_9N$ 267.0671, obsv'd. 267.0655.

3.7. Preparation of 1-(2,3,5,6-tetrafluoropyridyl)-3-methyl-2-butene, 2

Similarly, **2** was prepared from 0.75 g (5.0 mmol) of 4-bromo-2-methyl-2-butene in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 0.7 g (61%) of **2**, GLPC purity 98.4%. ^{19}F NMR: δ −92.3 (m, 2F), −145.3 (m, 2F); ^{1}H NMR: δ 1.7 (s, 3H), 1.8 (s, 3H), 3.5 (d, $^3J_{HH}$ = 7.4 Hz, 2H), 5.2 (tm, $^3J_{HH}$ = 7.5 Hz, 1H). ^{13}C NMR: δ 143.4 (dm, $^1J_{CF}$ = 243.9 Hz), 140.4 (dm, $^1J_{CF}$ = 253.8 Hz), 134.4 (tt, $^2J_{CF}$ = 17.1, $^3J_{CF}$ = 4.6 Hz), 136.5 (s), 117.1 (s), 22.9 (s), 25.7 (s),

17.7 (s). FTIR: (CCl_4, cm^{-1}) 2917.6 (w), 1645.2 (m), 1472.0 (s), 1254.2 (m). GC–MS: *m/z* (relative intensity) 219 (M^+, 100.0), 204 (70.4), 184 (68.6), 277 (47.3), 164 (46.7), 69 (14.8). HRMS: calc'd. for $C_{10}F_4H_9N$ 219.0671, obsv'd. 219.0672.

3.8. Preparation of 3-(2,3,5,6-tetrafluoropyridyl)cyclohexene, 3

Similarly, **3**, was prepared from 0.8 g (5.0 mmol) of 3-bromocyclohexene in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 0.95 g (82%) of **3** as a clear liquid, GLPC purity 100.0%. ^{19}F NMR: δ −92.4 (m, 2F), −144.6 (m, 2F). ^1H NMR: δ 1.8 (m, 2H), 2.0 (m, 2H), 2.1 (m, 2H), 4.0 (m, 1H), 5.6 (dm, $^3J_{HH}$ = 10.0 Hz, 1H), 5.9 (m, 1H); ^{13}C NMR: δ 143.6 (dm, $^1J_{CF}$ = 242.7 Hz), 140.8 (dm, $^1J_{CF}$ = 250.7 Hz), 138.5 (tt, $^2J_{CF}$ = 18.0 Hz, $^3J_{CF}$ = 4.6 Hz), 129.5 (s), 125.2 (s), 33.6 (s), 28.1 (s), 24.3 (s), 22.1 (s). FTIR: (CCl_4, cm^{-1}) 1469.5 (s), 958.7 (m). GC–MS: *m/z* (relative intensity) 231 (M^+, 68.1), 216 (100.0), 202 (31.2), 183 (46.0), 170 (29.2), 54 (78.7).

3.9. Preparation of (Z)-4-(2,3,5,6-tetrafluoropyridyl)-2-pentene, 4

Similarly, **4** was prepared from 0.5 g (5.0 mmol) of (*Z*)-4-chloro-2-pentene in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 0.8 g (74%) of **4**, GLPC purity 99.4%. ^{19}F NMR: δ −92.4 (m, 2F), −144.9 (m, 2F). ^1H NMR: δ 1.5 (d, $^3J_{HH}$ = 6.9 Hz, 3H), 1.7 (d, $^3J_{HH}$ = 4.5 Hz, 3H), 4.0 (m, 1H), 5.6 (m, 2H). ^{13}C NMR: δ 143.9 (dm, $^1J_{CF}$ = 259.0 Hz), 140.5 (dm, $^1J_{CF}$ = 264.6 Hz), 130.2 (m), 130.4 (s), 127.9 (s), 34.6 (s), 18.9 (s), 17.6 (s).

3.10. Preparation of 1-(2,3,5,6-tetrafluoropyridyl)-1,2-propadiene 6

Similarly, **6** was prepared from 1.0 g (7.0 mmol) of propargyl tosylate in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 0.6 g (63%) of **6**, GLPC purity 100.0%. ^{19}F NMR: δ −92.7 (m, 2F), −144.6 (m, 2F). ^1H NMR: δ 6.3 (t, $^4J_{HH}$ = 6.9 Hz, 1H), 5.3 (d, $^4J_{HH}$ = 6.9 Hz, 2H); ^{13}C NMR: 214.5 (s), 143.5 (dm, $^1J_{CF}$ = 243.8 Hz), 139.1 (dm, $^1J_{CF}$ = 261.6 Hz), 127.5 (tm, $^2J_{CF}$ = 11.6 Hz). 80.1 (t, $^3J_{CF}$ = 2.8 Hz), 78.7 (s). FTIR: (CCl_4, cm^{-1}): 1933.1 (w, C=C=C), 1639.8 (m), 1476.7 (s), 1423.7 (m). GC–MS: *m/z* (relative intensity) 189 (M^+, 100.0), 170 (31.1), 162 (15.1). HRMS: calc'd. for $C_8F_4H_3N$ 189.0202, obsv'd. 189.0188.

3.11. Preparation of (E)-1-(2,3,5,6-tetrafluoropyridyl)pentafluoropropene, 7

Similarly, **7** was prepared from 1.3 g (5.0 mmol) of (*Z*)-1-iodo-1-pentafluoropropene in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.2 g (85%) of **7**, GLPC purity 99.5%. ^{19}F NMR: δ −68.7 (dd, $^3J_{FF}$ = 20.4, $^4J_{FF}$ = 10.2 Hz, 3F), −87.9 (m, 2F), −137.5 (m, 2F), −141.7 (dm, $^3J_{FF}$ = 140.0 Hz, 1F), −157.0 (dm, $^3J_{FF}$ = 140.0 Hz, 1F). ^{13}C NMR: δ 144.5 (dm, $^1J_{CF}$ = 245.1 Hz), 142.6 (ddm, $^1J_{CF}$ = 259.7 Hz, $^2J_{CF}$ = 42.3 Hz), 140.9 (ddm, $^1J_{CF}$ = 260.9 Hz, $^2J_{CF}$ = 46.3 Hz), 140.1 (dm, $^1J_{CF}$ = 276.4 Hz), 119.9 (m), 118.6 (qdd, $^1J_{CF}$ = 273.4 Hz, $^2J_{CF}$ = 35.3 Hz, $^3J_{CF}$ = 4.6 Hz). FTIR: (CCl_4, cm^{-1}): 1481.1 (s), 1380.8 (m), 1223.5 (s), 1170.7 (s), 967.9 (m). GC–MS: *m/z* (relative intensity) 281 (M^+, 4.8), 117 (100.0), 105 (20.6). HRMS: calc'd. for C_8F_9N 280.9887, obsv'd. 280.9879.

3.12. Preparation of (E)-1-(2,3,5,6-tetrafluoropyridyl)-1-hexene, 8

Similarly, **8** was prepared from 1.3 g (6.0 mmol) of (*E*)-1-iodo-1-hexene in 4 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.0 g (85%) of **8**, GLPC purity 98.3%. ^{19}F NMR: δ −93.1 (m, 2F), −146.4 (m, 2F). ^1H NMR: δ 0.9 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 1.4 (m, 2H), 1.5 (m, 2H), 2.3 (m, 2H), 6.4 (d, $^3J_{HH}$ = 16.3 Hz, 1H), 6.9 (dt, $^3J_{HH}$ = 16.3 Hz, $^3J_{HH}$ = 7.0 Hz, 1H). ^{13}C NMR: δ 147.3 (t, $^3J_{CF}$ = 7.6 Hz), 144.1 (dm, $^1J_{CF}$ = 257.5 Hz), 139.7 (dm, $^1J_{CF}$ = 259.1 Hz), 129.9 (tt, $^2J_{CF}$ = 12.1 Hz, $^3J_{CF}$ = 5.5 Hz), 114.9 (m), 34.6 (s), 31.0 (s), 22.6 (s), 14.0 (s). FTIR: (CCl_4, cm^{-1}): 1639.1 (m), 1470.9 (s), 977.9 (m). GC–MS: *m/z* (relative intensity) 233 (M^+, 8.8), 204 (4.4), 177 (100.0), 69 (21.5), 56 (37.1).

3.13. Preparation of ethyl 2-(2,3,5,6-tetrafluoropyridyl)benzoate, 10

Similarly, **10** was prepared from 1.4 g (5.0 mmol) of ethyl-2-iodobenzoate in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.2 g (80%) of **10**, mp 73–74 °C. ^{19}F NMR: δ −92.1 (m, 2F), −143.8 (m, 2F); ^1H NMR: δ 1.2 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 4.3 (q, $^3J_{HH}$ = 7.1 Hz, 2H), 7.3 (dm, $^3J_{HH}$ = 7.5 Hz, 1H), 7.6 (m, 2H) 8.2 (dm, $^3J_{HH}$ = 7.8 Hz. 1H); ^{13}C NMR: δ 165.5 (s), 143.4 (dm, $^1J_{CF}$ = 243.9 Hz), 139.4 (dm, $^1J_{CF}$ = 256.7 Hz), 134.8 (tt, $^2J_{CF}$ = 17.1 Hz, $^3J_{CF}$ = 3.3 Hz), 132.7 (s), 131.5 (s), 131.0 (s), 130.6 (s), 130.3 (s), 126.9 (s), 61.7 (s), 13.9 (s). FTIR: (CCl_4, cm^{-1}): 1727.7 (s, C=O), 1645.8 (m), 1468.9 (s), 1269.3 (s), 1158.3 (m), 1081.0 (m), 957.1 (m). GC–MS: *m/z* (relative intensity) 299 (M^+, 34.3), 254 (63.4), 251 (100.0), 226 (26.4), 223 (28.6), 207 (26.7), 171 (23.1), 150 (15.4). HRMS: calc'd. for $C_{14}F_4H_9NO_2$ 299.0569, obsv'd. 299.0560.

3.14. Preparation of (E)-1,1,1,2,2,3,3-heptafluoro-5-(2.3,5,6-tetrafluoropyridyl)-4-nonene, 9

Similarly, **9** was prepared from 1.9 g (7.0 mmol) of (*E*)-1,1,1,2,2,3,3-heptafluoro-5-iodo-4-nonene in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.8 g (91%) of **9** as a liquid, GLPC purity 100.0%. ^{19}F NMR: δ −143.2 (m, 2F), −128.3 (s, 2F), −108.2 (m, 2F), −89.7 (m, 2F), −80.8 (t, $^4J_{FF}$ = 8.7 Hz, 3F); ^1H NMR: δ 0.9 (t, $^3J_{HH}$ = 6.7 Hz, 3H), 1.3 (m, 4H), 2.7 (m, 2H), 5.7 (t, $^3J_{HF}$ = 14.5 Hz, 1H); ^{13}C NMR: δ 143.8 (dm, $^1J_{CF}$ = 246.8 Hz), 143.3 (s), 139.1 (dm, $^1J_{CF}$ = 259.7 Hz), 133.5 (t, $^2J_{CF}$ = 16.5 Hz), 121.3 (t, $^2J_{CF}$ = 24.1 Hz), 117.9 (qt, $^1J_{CF}$ = 287.0, $^2J_{CF}$ = 34.1 Hz), 114.0 (tt, $^1J_{CF}$ = 254.1 Hz, $^2J_{CF}$ = 31.2 Hz), 108.9 (triplet of sextet, $^1J_{CF}$ = 264.9 Hz, $^2J_{CF}$ = 37.7 Hz), 31.5 (s), 30.1 (s), 22.5 (s), 13.4 (s). FTIR: (CCl_4, cm^{-1}): 1468.2 (s), 1231.3 (s), 1180.8 (m), 1116.1 (m), 971.8 (m). GC–MS: *m/z* (relative intensity) 401 (M^+, 17.4), 359 (100.0).

3.15. Preparation of 1-(2,3,5,6-tetrafluoropyridine)-1-propanone, 11

Similarly, **11** was prepared from 0.5 g (5.0 mmol) of propionyl chloride in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 0.8 g (77%) of **11**, GLPC purity 98.7%. ^{19}F NMR: δ −88.8 (m, 2F), −143.6 (m, 2F); ^1H NMR: δ 1.3 (t, $^3J_{HH}$ = 7.2 Hz, 3H), 2.9 (q, $^3J_{HH}$ = 7.2 Hz, 2H); ^{13}C NMR: δ 194.0 (m), 143.4 (dm, $^1J_{CF}$ = 247.8 Hz), 138.3 (dm, $^1J_{CF}$ = 262.1 Hz), 131.9 (t, $^2J_{CF}$ = 18.3 Hz), 37.9 (s), 6.6 (s). FTIR: (CCl_4, cm^{-1}): 1729.4 (m, C=O), 1466.8 (s), 1269.2 (m), 956.4 (m). GC–MS: *m/z* (relative intensity) 207 (M^+, 44.9), 178 (100.0), 150 (38.0), 57 (83.3).

3.16. Preparation of methyl-4-(2,3,5,6-tetrafluoropyridyl)-4-oxo-butanoate, 12

Similarly, **12** was prepared from 0.75 g (5.0 mmol) of 3-carbomethoxypropionyl chloride in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.1 g (83%) of **12**, GLPC purity 98.6%. ^{19}F NMR: δ −88.5 (m, 2F), −142.9 (m, 2F); ^1H NMR: δ 2.8 (t, $^3J_{HH}$ = 6.5 Hz, 2H), 3.2 (t, $^3J_{HH}$ = 6.5 Hz, 2H), 3.7 (s, 3H); ^{13}C NMR: δ 192.4 (s), 172.4 (s), 144.1 (dm, $^1J_{CF}$ = 247.8 Hz), 139.1 (dm, $^1J_{CF}$ = 264.0 Hz), 131.4 (t, $^2J_{CF}$ = 17.0 Hz), 52.2 (s), 39.5 (s), 27.8 (s). FTIR: (CCl_4, cm^{-1}): 1740.9 (m, C=O), 1468.4 (s), 1274.5 (m). GC–MS: *m/z* (relative intensity) 265 (M^+, 12.9), 234 (53.5), 178 (100.0), 150 (18.5), 115 (10.9). HRMS: calc'd. for $C_{10}F_4H_7NO_2$ 265.0362, obsv'd. 265.0361.

3.17. Preparation of 4-benzoyl-2,3,5,6-tetrafluoropyridine, 13

Similarly, **13** was prepared from 0.7 g (5.0 mmol) of benzoyl chloride in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.0 g (78%) of **13**, GLPC purity 100.0%. ^{19}F NMR: δ −88.9 (m, 2F), −142.3 (m, 2F); ^{1}H NMR: δ 7.5 (t, $^{3}J_{HH}$ = 7.6 Hz, 2H), 7.7 (tm, $^{3}J_{HH}$ = 7.4 Hz, 1H), 7.9 (d, $^{3}J_{HH}$ = 8.1 Hz, 2H); ^{13}C NMR: δ 184.6 (s), 143.8 (dm, $^{1}J_{CF}$ = 247.0 Hz), 138.2 (dm, $^{1}J_{CF}$ = 262.1 Hz), 131.9 (t, $^{2}J_{CF}$ = 19.6 Hz), 129.9 (s), 135.9 (s), 135.0 (s) 129.6 (s). FTIR: (CCl_4, cm^{-1}): 1693.4 (s, C=O), 1491.9 (m), 1648.0 (s), 1418.0 (m), 1318.8 (m), 1288.6 (s), 969.1 (m), 832.7 (m). GC–MS: *m*/*z* (relative intensity) 255 (M^+, 62.8), 105 (100.0), 77 (67.3).

3.18. Preparation of 4-(2-bromobenzoyl)-2,3,5,6-tetrafluoropridine, 14

Similarly, **14** was prepared from 1.1 g (5.0 mmol) of 2-bromobenzoyl chloride in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.4 g (85%) of **14** as a white solid, mp: 74–75 °C. ^{19}F NMR: δ −88.9 (m, 2F), −142.6 (m, 2F); ^{1}H NMR: δ 7.6 (m, 2H), 7.7 (m, 2H); ^{13}C NMR: δ 184.8 (s), 143.6 (dm, $^{1}J_{CF}$ = 248.1 Hz), 129.1 (dm, $^{1}J_{CF}$ = 264.8 Hz), 131.6 (m), 137.1 (s), 134.7 (s), 131.9 (s), 128.2 (s), 127.7 (s), 121.1 (s). FTIR: (CCl_4, cm^{-1}) 1687.8 (w, C=O), 1466.7 (s), 1297.1 (m), 970.8 (m). GC–MS: *m*/*z* (relative intensity) 335 (M^+, 22.8), 333 (M^+, 23.5), 254 (6.9), 185 (98.8), 183 (100.0), 157 (33.4), 155 (34.5). HRMS: calc'd. for $C_{12}F_4H_4NO^{79}Br$ 332.9412, obsv'd. 332.9419.

3.19. Preparation of 4-(4-bromobenzoyl)-2,3,5,6-tetrafluoropyridine, 15

Similarly, **15** was prepared from 1.1 g (5.0 mmol) of 4-bromobenzoyl chloride in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.2 g (72%) of **15** as a white solid, mp: 85–86 °C. ^{19}F NMR: δ −88.3 (m, 2F), −141.9 (m, 2F); ^{1}H NMR 7.7 (m, 4H); ^{13}C NMR: δ 183.5 (s), 143.7 (dm, $^{1}J_{CF}$ = 252.5 Hz), 138.6 (dm, $^{1}J_{CF}$ = 262.7 Hz), 131.3 (m), 133.6 (s), 132.9 (s), 131.6 (s), 131.1 (s). FTIR: (CCl_4, cm^{-1}): 1690.5 (s, C=O), 1588.5 (m), 1467.7 (s), 1287.6 (m), 1071.8 (m), 949.9 (m). GC–MS: *m*/*z* (relative intensity) 335 (M^+, 45.4), 333 (41.6), 185 (100.0), 183 (82.3), 157 (38.3), 155 (42.7), 150 (16.6), 76 (41.1).

3.20. Preparation of (E)-3-phenyl-1-(2,3,5,6-tetrafluoropyridyl)-2-propene-1-one, 16

Similarly, **16** was prepared from 0.83 g (5.0 mmol) of (*E*)-cinnamoyl chloride in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.3 g (93%) of **16** as a white solid, mp: 87–88 °C. ^{19}F NMR: δ −88.8 (m, 2F), −142.6 (m, 2F); ^{1}H NMR: δ 7.0 (dm, $^{3}J_{HH}$ = 16.2 Hz, 1H), 7.4–7.6 (m, 6H); ^{13}C NMR: δ 183.3 (s), 150.1 (s), 143.8 (dm, $^{1}J_{CF}$ = 236.8 Hz), 138.9 (dm, $^{1}J_{CF}$ = 262.7 Hz), 131.8 (t, $^{2}J_{CF}$ = 18.0 Hz), 133.3 (s), 132.3 (s), 129.3 (s), 129.2 (s), 125.3 (s). FTIR: (CCl_4, cm^{-1}): 1671.6 (s, C=O), 1625.8 (m), 1606.6 (m), 1466.2 (s), 1450.9 (m), 1409.4 (m), 1287.6 (s), 1261.9 (m), 976.2 (m). GC–MS: *m*/*z* (relative intensity) 281 (M^+, 54.1), 280 (100.0), 131 (49.3), 103 (74.6), 77 (53.4).

3.21. Preparation of 1-(2,3,5,6-tetrafluoropridyl)-1-hexyne, 17

Similarly, **17** was prepared from 1.4 g (7.0 mmol) of 1-iodohexyne in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.0 g (87%) of **17** as a clear liquid, GLPC purity 100.0%. ^{19}F NMR: δ −91.6 (m, 2F), −139.8 (m, 2F); ^{1}H NMR: δ 1.0 (t, $^{3}J_{HH}$ = 7.3 Hz, 3H), 1.5 (m, 2H), 1.6 (m, 2H), 2.6 (t, $^{3}J_{HH}$ = 7.1 Hz, 2H); ^{13}C NMR: δ 143.8 (dm, $^{1}J_{CF}$ = 244.3 Hz), 142.7 (dm, $^{1}J_{CF}$ = 262.5 Hz), 118.2 (tt, $^{2}J_{CF}$ = 16.7 Hz, $^{3}J_{CF}$ = 4.5 Hz), 110.4 (t, $^{4}J_{CF}$ = 3.2 Hz), 65.6 (t, $^{3}J_{CF}$ = 3.8 Hz), 30.3 (s), 22.2 (s), 19.9 (s), 13.6 (s). FTIR: (CCl_4, cm^{-1}): 2250.8 (w, C≡C), 1638.3 (m), 1470.0 (s), 962.9 (m). GC–MS: *m*/*z* (relative intensity) 231 (M^+, 3.3), 216 (100.00), 188 (20.9). HRMS: calc'd. for $C_{11}F_4H_9N$ 231.0671, obsv'd. 231.0678.

3.22. Preparation of 1-(2,3,5,6-tetrafluoropyridyl)-3-methoxy-1-propyne, 18

Similarly, **18** was prepared from 1.4 g (7.0 mmol) of 1-iodo-3-methoxypropyne in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 0.9 g (82%) of **18** as a liquid, GLPC purity 100.0%. ^{19}F NMR: δ −90.6 (m, 2F), −138.6 (m, 2F); ^{1}H NMR: δ 3.5 (s, 3H), 4.4 (s, 2H); ^{13}C NMR: δ 143.8 (dm, $^{1}J_{CF}$ = 245.1 Hz), 142.6 (dm, $^{1}J_{CF}$ = 164.4 Hz), 117.0 (tt, $^{2}J_{CF}$ = 16.6 Hz, $^{3}J_{CF}$ = 4.5 Hz), 103.8 (t, $^{4}J_{CF}$ = 3.4 Hz), 70.8 (t, $^{3}J_{CF}$ = 3.9 Hz), 60.4 (s), 58.2 (s). FTIR: (CCl_4, cm^{-1}): 2250.8 (C≡C), 1638.9 (m), 1471.1 (s), 1095.8 (m), 964.3 (m). GC–MS: *m*/*z* (relative intensity) 219 (M^+, 6.2), 204 (3.3), 188 (100.0), 175 (7.5), 150 (4.4), 69 (21.7).

3.23. Preparation of 3-(1-ethoxyethoxy)-1-(2,3,5,6-tetrafluoropyridyl)-propyne, 19

Similarly, **19** was prepared from 1.8 g (7.0 mmol) of 3-(1-ethoxyethoxy)-1-iodopropyne in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.0 g (71%) of **19** as a white solid, mp: 52–56 °C. ^{19}F NMR: δ −90.8 (m, 2F), −138.6 (m, 2F); ^{1}H NMR: δ 1.2 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H), 1.4 (d, $^{3}J_{HH}$ = 5.3 Hz, 3H), 3.7–3.5 (m, 2H), 4.3 (s, 2H), 4.9 (q, $^{3}J_{HH}$ = 5.3 Hz, 1H); ^{13}C NMR: δ 143.9 (dm, $^{1}J_{CF}$ = 245.1 Hz), 142.6 (dm, $^{1}J_{CF}$ = 264.5 Hz), 117.0 (tt, $^{2}J_{CF}$ = 16.3 Hz, $^{3}J_{CF}$ = 4.7 Hz), 104.5 (t, $^{4}J_{CF}$ = 3.4 Hz), 70.0 (t, $^{3}J_{CF}$ = 3.8 Hz), 99.6 (s), 61.6 (s), 52.9 (s), 19.8 (s), 15.4 (s). FTIR: (CCl_4, cm^{-1}): 2254.5 (w, C≡C), 1638.5 (m), 1471.1 (s), 1104.4 (m), 964.3 (m). GC–MS: *m*/*z* (relative intensity) 205 ($M^+ - C_4H_9O$, 50.3), 204 (45.5), 188 (35.0), 186 (27.2), 157 (29.5), 156 (40.5), 106 (27.2).

3.24. Preparation of (2,3,5,6-tetrafluoropyridyl)-(1-cyclohexenyl)ethyne, 20

Similarly, **20** was prepared from 1.8 g (7.7 mmol) of 1-iodo-2-(1-cyclohexenyl)ethyne in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.1 g (85%) of **20** as a white solid, mp: 64–65 °C. ^{19}F NMR: δ −91.6 (m, 2F), −139.5 (m, 2F); ^{1}H NMR: δ 1.7 (m, 4H), 2.2 (m, 4H), 6.5 (m, 1H); ^{13}C NMR: δ 143.5 (dm, $^{1}J_{CF}$ = 244.7 Hz), 141.8 (dm, $^{1}J_{CF}$ = 262.7 Hz), 141.1 (s), 119.6 (s), 118.1 (tt, $^{2}J_{CF}$ = 16.7 Hz, $^{3}J_{CF}$ = 4.5 Hz), 109.1 (t, $^{4}J_{CF}$ = 3.0 Hz), 71.2 (t, $^{3}J_{CF}$ = 4.3 Hz), 28.4 (s), 26.1 (s), 22.1 (s), 21.2 (s). FTIR: (CCl_4, cm^{-1}): 2941.7 (m), 2211.6 (m, C≡C), 1621.2 (m), 1473.5 (s), 1182.3 (m), 943.7 (m). GC–MS: *m*/*z* (relative intensity) 255 (M^+, 100.0), 239 (25.0), 208 (51.3), 191 (19.9), 151 (34.3), 128 (93.6), 94 (54.2).

3.25. Preparation of 1-(2,3,5,6-tetrafluoropyridyl)-2-phenylethyne, 21

Similarly, **21** was prepared from 1.8 g (8.0 mmol) of 1-iodo-2-phenylethyne in 5 mL of dry DMF and (5.0 mmol) of **1**. Usual work-up gave 1.1 g (91%) of **21** as a white solid, mp: 120–121 °C. ^{19}F NMR: δ −91.1 (m, 2F), −138.8 (m, 2F); ^{1}H NMR: δ 7.4 (m, 3H), 7.6 (m, 2H); ^{13}C NMR: δ 143.6 (dm, $^{1}J_{CF}$ = 242.2 Hz), 141.9 (dm, $^{1}J_{CF}$ = 263.8 Hz), 132.4 (s), 130.7 (s), 128.8 (s), 120.6 (s), 117.5 (tt, $^{2}J_{CF}$ = 16.2 Hz, $^{3}J_{CF}$ = 4.2 Hz), 106.7 (t, $^{4}J_{CF}$ = 3.4 Hz), 73.5 (t, $^{3}J_{CF}$ = 3.8 Hz). FTIR: (CCl_4, cm^{-1}): 2224.7 (m, C≡C), 1635.9 (m), 1455.2 (s). GC–MS: *m*/*z* (relative intensity) 251 (M^+, 100.0).

3.26. Preparation of 2 via the phosphoniumtetrafluorobroate methodology

In a typical experimental procedure, a dry 50 mL, two-necked, round-bottomed flask equipped with a septum port, a Teflon

coated stir-bar, and a water condenser topped with a nitrogen inlet, was charged with 3.1 g (7.0 mmol) of 4-tetrafluoropyridyl-tributylphosphonium tetrafluoroborate, 1.1 g (10.0 mmol) of Na_2CO_3, 1.0 g (7.0 mmol) of Cu(I)Br, and 15 mL of DMF. The solution was stirred under a nitrogen atmosphere, then 0.8 g (5.3 mmol) of 4-bromo-2-methyl-2-butene was added to the reaction mixture and stirred overnight at room temperature. The reaction mixture was loaded onto a chromatography column packed with silica gel, and the product was eluted with hexane/CH_2Cl_2 (8/2). Thin-layer chromatography was used to monitor the fractionation. The fraction which contained the product was concentrated by rotary evaporation. Any last traces of solvent were removed under vacuum. The yield was 0.7 g (64%) of **2**, GLPC purity 100%.

3.27. Preparation of 3 via the phosphonium tetrafluoroborate methodology

Similarly, **3** was prepared from 3.1 g (7.0 mmol) of 4-tetrafluoropyridyltributylphosphoniumtetrafluoroborate, 1.1 g (10.0 mmol) of Na_2CO_3, 1.0 g (7.0 mmol) of Cu(I)Br, 15 mL of DMF, and 0.8 g (5.0 mmol) of 3-bromo-1-cyclohexene. Usual work-up gave 0.8 g (69%) of **3**, GLPC purity 97%.

3.28. Preparation of 16 via the phosphoniumtetrafluoroborate methodology

Similarly, **16** was prepared from 3.1 g (7.0 mmol) of 4-tetrafluoropyridyltributylphosphoniumtetrafluoroborate. 1.1 g (10.0 mmol) of Na_2CO_3, 1.0 g (7.0 mmol) of Cu(I)Br, 15 mL of DMF, and 0.8 g (5.0 mmol) of (*E*)-cinnamoyl chloride. Usual work-up gave 1.1 g (78%) of **16**.

3.29. Preparation of 4-[2,3,5,6-(tetrafluoropyridyl)]-benzoyl-2,3,5,6 tetrafluoropyridine 26 via the phosphonium tetrafluoroborate methodology

Similarly, **26** was prepared from 3.1 g (7.0 mmol) of 4-tetrafluoropyridltributylphosphoniumtetrafluoroborate, 1.1 g (10.0 mmol) of Na_2CO_3, 1.0 g (7.0 mmol) of Cu(I)Br, 15 mL of DMF and 1.1 g (5.0 mmol) of 2-bromobenzoyl chloride. Usual work-up gave 0.5 g (49%) of **26** as a light yellow solid, mp: 154–156 °C. ^{19}F NMR: −87.8 (m, 2F), −90.9 (m, 2F), −141.5 (m, 2F), −143.7 (m, 2F); ^{1}H NMR: 7.5 (d, *J* = 7.6 Hz, 1H), 7.7 (m, 2H), 7.9 (td, $^3J_{HH}$ = 7.3 Hz, $^4J_{HH}$ = 1.5 Hz, 1H); ^{13}C NMR: 184.2 (s), 143.9 (dm, $^1J_{CF}$ = 246.6 Hz), 138.6 (dm, $^1J_{CF}$ = 264.8 Hz), 135.1 (s), 134.2 (s), 132.8 (m), 132.5 (s), 132.2 (s), 131.2 (s), 130.4 (tm, $^2J_{CF}$ = 18.6 Hz), 126.4 (s). FTIR: 1699.9 (w, C=O), 1471.4 (s). GC–MS: *m*/*z* (relative intensity) 404 (M^+, 50.3), 385 (12.3), 254 (100.0), 226 (40.6), 206 (33.7), 150 (17.3).

3.30. Preparation of 15 via the phosphonium tetrafluoroborate methodology

Similarly, **15** was prepared from 3.1 g (7.0 mmol) of 4-tetrafluoropyridyltributyl-phosphoniumtetrafluoroborate, 1.1 g (10.0 mmol) of Na_2CO_3, 1.0 g (7.0 mmol) of Cu(I)Br, 15 mL of DMF, and 1.1 g (5.0 mmol) of 4-bromobenzoyl chloride. Usual work-up gave 1.1 g (66%) of **15**.

3.31. Preparation of 1-(2,3,5,6-tetrafluoropyridyl)-2-phenylethyne, 21 via Pd coupling

A dry 50 mL, two-necked flask, equipped with a rubber septum, a Teflon coated stir bar and a water condenser topped with a nitrogen inlet, was charged with 1.2 g (12.0 mmol) of phenylacetylene, 2.8 g (10.0 mmol) of 4-iodo-2,3,5,6-tetrafluoropyridine, 0.18 g, 5.0 mol.% of $PdCl_2(PPh_3)_2$, 0.03 g (3.0 mol.%) of Cu(I)I and 20 mL of Et_3N. The solution was stirred under a N_2 atmosphere and heated overnight at 70 °C. After complete consumption of the iodopyridine (determined by ^{19}F NMR analysis of the reaction mixture), the reaction mixture was cooled to RT, gravity filtered, and the solid was washed with 20 mL CH_2Cl_2. The filtrate was concentrated by rotary evaporation, loaded onto a silica-gel chromatography column and the product eluted with hexane. Thin-layer chromatography was used to monitor the fractionation. The fraction that contained the product was concentrated by rotary evaporation; any last traces of solid were removed under vacuum. The yield of **21** (white solid) was 2.2 g (88%). The data was similar to the data reported in 3.25. GC–MS: (*m*/*z*) (relative intensity): 251 (M^+, 100.0). HRMS: calc'd. for $C_{13}F_4H_4N$ 251.0358; obsv'd. 251.0373.

3.32. Preparation of 1-(2,3,56-tetrafluoropyridyl)-2-(1-aminocyclohexyl)ethyne, 22

Similar to 3.31, 1.5 g (12.0 mmol) of 1-ethynylcyclohexylamine, 2.8 g (10.0 mmol) of 4-iodotetrafluoropyridine, 0.18 g (5.0 mol.%) of $PdCl_2(PPh_3)_2$, 0.03 g (3.0 mol.%) Cu(I)I and 20 mL of Et_3N gave after chromatography (CH_2Cl_2/acetone, 8/2) 2.0 g (73%), GLPC purity, 100%, of liquid **22**. ^{19}F NMR: δ −91.3 (m, 2F), −139.2 (m, 2F); ^{1}H NMR: δ 1.2–1.8 (m, 10H), 2.0 (m, 2H); ^{13}C NMR: ($CDCl_3$, TMS): δ 143.2 (dm, $^1J_{CF}$ = 244.6 Hz), 141.7 (dm, $^1J_{CF}$ = 263.1 Hz), 117.3 (tt, $^2J_{CF}$ = 16.2 Hz, $^3J_{CF}$ = 3.9 Hz), 114.5 (t, $^4J_{CF}$ = 2.9 Hz), 67.2 (t, $^3J_{CF}$ = 4.1 Hz), 50.6 (s), 39.5 (s), 24.9 (s), 22.9 (s). FTIR: (CCl_4, cm^{-1}): 2938.7 (m), 2222.5 (w, C≡C), 1637.4 (m), 1469.8 (s), 964 (m). GC–MS (*m*/*z*) (relative intensity): 272 (M^+, 0.9), 243 (16.1), 229 (100.0), 216 (12.6), 201 (13.6). HRMS: calc'd. for $C_{13}F_4H_{12}N_2$ 272.0937; obsv'd. 272.0927.

3.33. Preparation of 1-(2,3,5,6-tetrafluoropridyl)-2-(1-hydroxycyclohexyl) ethyne, 23

Similar to 3.31, 1.5 g (12.0 mmol) of 1-ethynyl-1-cyclohexanol, 2.8 g (10.0 mmol) of 4-iodotetrafluoropyridine, 0.18 g (5.0 mol.%) of $PdCl_2(PPh_3)_2$, 0.03 g (3.0 mol.%) Cu(I)I and 20 mL of Et_3N gave, after chromatography (ether/CH_2Cl_2, 2/8), 2.0 g (73% of **23** as a white solid, mp 67–68 °C. ^{19}F NMR: δ −90.8 (m, 2F), −138.7 (m, 2F); ^{1}H NMR: 1.3–2.2 (m, 10H), 2.3 (s, 1H); ^{13}C NMR: δ 143.4 (dm, $^1J_{CF}$ = 245.3 Hz), 142.0 (dm, $^1J_{CF}$ = 263.9 Hz), 116.9 (tm, $^2J_{CF}$ = 16.1 Hz), 111.1 (t, $^4J_{CF}$ = 3.3 Hz), 68.7 (t, $^3J_{CF}$ = 10.9 Hz), 69.5 (s), 39.3 (s), 24.9 (s), 23.1 (s). FTIR: CCl_4, cm^{-1}): 2940.9 (m), 2236.4 (w, C≡C), 1638 (m), 1469.7 (s), 1069.4 (m), 966.2 (s). GC–MS *m*/*z* (relative intensity): 273 (M^+, 1.6), 255 (11.7), 230 (59.3), 217 (62.2), 202 (36.2), 188 (25.9), 175 (30.1), 149 (47.7), 55 (71.9), 40 (100.0). HRMS: calc'd. for $C_{13}F_4H_{11}NO$ 273.0777, obsv'd. 273.0774.

3.34. Preparation of 4-(2,3,5,6-tetrafluoropyridyl)-2-methyl-3-butyne-2-ol, 24

Similar to 3.31, 1.0 g (12.0 mmol) of 2-methyl-3-butyne-2-ol, 2.8 g (10.0 mmol) of 4-iodotetrafluoropyridine, 0.18 g (5.0 mol.%) of $PdCl_2(PPh_3)_2$, 0.03 g (3.0 mol.%) Cu(I)I and 20 mL of Et_3N, gave after chromatography (CH_2Cl_2), 2.1 g (92%) of **24** as a white solid, mp 56–58 °C, ^{19}F NMR: δ −91.1 (m, 2F), −138.9 (m, 2F); ^{1}H NMR: δ 1.7 (s, 6H), 3.4 (s, 1H); ^{13}C NMR ($CDCl_3$, TMS): δ 143.4 (dm, $^1J_{CF}$ = 245.2 Hz), 142.2 (dm, $^1J_{CF}$ = 264.2 Hz), 117.2 (tt, $^2J_{CF}$ = 16.0 Hz, $^3J_{CF}$ = 4.6 Hz), 111.9 (t, $^4J_{CF}$ = 3.4 Hz), 66.7 (t, $^3J_{CF}$ = 3.7 Hz), 66.1 (s). 30.2 (s). FTIR: (CCl_4, cm^{-1}): 2238.6 (w, C≡C), 1637.7 (m), 1469.9 (s), 966.2 (m). GC–MS: (*m*/*z*) (relative intensity): 233 (M^+, 1.4), 218 (100.0), 175 (13.0), 43 (67).

3.35. Preparation of (Z)-1-methoxy-4-(2,3,5,6-tetrafluoropyridyl)-1-butene-3-yne, **25**

Similar to 3.31, 1.0 g (12.0 mmol) of (*Z*)-1-methoxy-1-butene-3-yne, 2.8 g (10.0 mmol) of 4-iodotetrafluoropyridine, 0.18 g (5.0 mol.%) of $PdCl_2(PPh_3)_2$, 0.03 g (3.0 mol.%) Cu(I)I and 20 mL Et_3N gave, after chromatography (petroleum ether), 0.8 g (35%) of **25** as a white solid, mp 45–47 °C, ^{19}F NMR: δ −91.8 (m, 2F), −139.6 (m, 2F); ^{1}H NMR: δ 3.9 (s, 3H), 4.8 (d, $^3J_{HH}$ = 6.5 Hz, 1H), 6.6 (d, $^3J_{HH}$ = 6.5 Hz, 1H); ^{13}C NMR: δ 160.5 (s), 143.5 (dm, $^1J_{CF}$ = 244.1 Hz), 141.5 (dm, $^1J_{CF}$ = 262.5 Hz), 118.2 (tt, $^2J_{CF}$ = 16.5 Hz, $^3J_{CF}$ = 4.6 Hz), 102.9 (t, $^4J_{CF}$ = 3.0 Hz), 83.4 (s), 76.8 (t, $^3J_{CF}$ = 4.0 Hz), 61.2 (s). FTIR: (cm^{-1}): 2204.7 (w, C≡C), 1619.1 (m), 1469.1 (s), 1121 (m), 962.2 (m). GC–MS: (*m*/*z*) (relative intensity): 232 (M^++1, 11.4), 231 (M^+, 100.0), 188 (97.0), 162 (13.1), 123 (13.7).

4. Conclusions

A new and improved preparation of 4-iodo-2,3,5,6-tetrafluoropyridine is described. The 4-iodo-2,3,5,6-tetrafluoropyridine is utilized for the *in situ* preparation of the 4-tetrafluoropridylcopper reagent *via* two methods This copper reagent readily undergoes reaction with allylic halides, vinyl iodides, aryl halides, acid chlorides and acetylenic iodides to stereospecificially afford the corresponding 4-tetrafluoropyridyl derivatives. An alternative route to the alkyne derivatives was developed *via* the Pd(0) catalyzed reaction of 4-iodotetrafluoroyridine with 1-alkynes.

Acknowledgements

We thank the National Science Foundation (NSF) for support of this research.

References

[1] R.E. Banks, W.T. Flowers, S.N. Khaffaf, J. Fluorine Chem. 53 (1991) 127–142.
[2] R.D. Chambers, F.G. Drakesmith, W.K.R. Musgrave, J. Chem. Soc. (1965) 5045–5048.
[3] C. Tamborski, G.J. Moore, J. Organomet. Chem. 26 (1971) 153–156.
[4] E.J. Soloski, W.E. Ward, C. Tamborski, J. Fluorine Chem. 2 (1972–1973) 361–371.
[5] R.E. Banks, R.N. Haszeldine, E. Phillips, I.M. Young, J. Chem. Soc. (C) (1967) 2091–2095.
[6] P.L. Heinze, T.D. Spawn, D.J. Burton, S. Shin-Ya, J. Fluorine Chem. 38 (1988) 131–134.
[7] P.L. Heinz, D.J. Burton, J. Fluorine Chem. 29 (1985) 359–361.
[8] D.J. Burton, Z.-Y. Yang, K.J. MacNeil, J. Fluorine Chem. 52 (1991) 251–255.
[9] K.J. MacNeil, D.J. Burton, J. Org. Chem. 58 (1993) 4411–4417.
[10] K.J. MacNeil, D.J. Burton, J. Org. Chem. 60 (1995) 4085–4089.
[11] B.V. Nguyen, D.J. Burton, J. Fluorine Chem. 67 (1994) 205–206.
[12] P. Sartori, H. Adelt, J. Fluorine Chem. 3 (1973–1974) 275–283.
[13] D.J. Burton, G.A. Hartgraves, J. Fluorine Chem. 128 (2007) 1198–1215.
[14] D.J. Burton, G.A. Hartgraves, J. Hsu, Tetrahedron Lett. 31 (1990) 3699–3702.
[15] Z.-Y. Yang, D.J. Burton, Tetrahedron Lett. 31 (1990) 1369–1372.
[16] B.V. Nguyen, Z.-Y. Yang, D.J. Burton, J. Fluorine Chem. 50 (1990) 265–270.
[17] Z.-Y. Yang, D.J. Burton, J. Fluorine Chem. 53 (1991) 307–326.
[18] B.V. Nguyen, Z.-Y. Yang, D.J. Burton, J. Org. Chem. 58 (1993) 7368–7376.