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FLUORINATED β-DIKETO PHOSPHORUS YLIDES: THEIR CYCLOCONDENSATION WITH AMIDINES AFFORDING 4-TRIFLUOROMETHYL- AND 4-PERFLUOROALKYL-SUBSTITUTED PYRIMIDINES

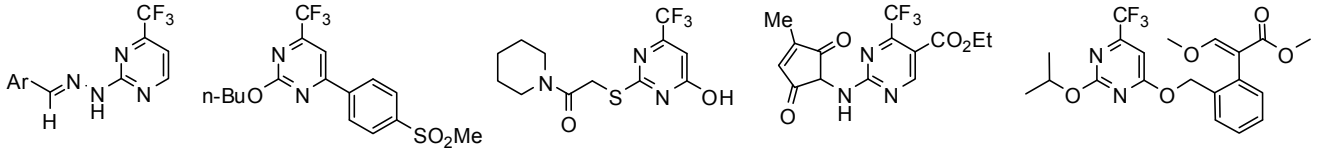
Ryosuke Saijo, Genki Watanabe, Ken-ichi Kurihara, and Masami Kawase*

Faculty of Pharmaceutical Sciences, Matsuyama University, 4-2 Bunkyo-cho, Matsuyama, Ehime 790-8578, Japan; E-mail: kawase@cc.matsuyama-u.ac.jp

Abstract – A study is presented for the syntheses of a series of 4-trifluoromethyl- and 4-perfluoroalkyl-substituted pyrimidines from the reaction of trifluoromethyl or perfluoroalkyl β-diketo phosphorus ylides ($Ph_3P{=}C(COR_F)COR$) with amidine hydrochloride.

INTRODUCTION

The pyrimidine ring has been known as an important framework in a large number of compounds having pharmaceutical and agricultural applications.[1] The heterocyclic core of pyrimidines is in general readily accessible *via* a [3+3] fragment approach of amidines and substrates containing 1,3-dielectrophilic centers, but methods are mostly related to the synthesis of nonfluorinated pyrimidines.[1] Introduction of a trifluoromethyl group and higher homologue C_nF_{2n+1} substituents into a heterocycle frequently results in compounds, which display more potent activity than the parent, probably due to the lipophilicity of the perfluoroalkyl substituents.[2] Thus, it would be very important to develop new efficient methodologies



Cruzain inhibitor[4a] COX-2 inhibitor[4b] Human A-FABP inhibitor[4c] Inhibitor of AP-1 and NF-κB mediated expression[4d] Antiproliferative Fluacrypyrim[4e]

Figure 1. Examples of biologically active 4-trifluoromethylpyrimidines

for the preparation of fluorinated pyrimidines, which would be strongly expected to present new bioactivities or functions (Figure 1).[3]

General methods for the preparation of these compounds involve the reactions of amidines with trifluoromethylated precursors such as 1-trifluoromethylated 1,3-diketones,[4a] α,β-unsaturated trifluoromethyl ketones,[4b] enamino(trifluoromethyl)ketones,[4c] α-trifluoroacetylpropanenitriles,[4d] and β-methoxyvinyl trifluoromethyl ketones.[4e] These 1,3-dielectrophiles are important precursors to the trifluoromethylated pyrimidines, however, the availability of diversity substituted 1,3-diketones is limited. Because pyrimidines are electron-deficient and generally low reactive in electrophilic substitution, the trifluoromethylation afforded a trace amount of certain trifluoromethylated products.[5] Till now, there have been limited methodologies for the preparation of trifluoromethylated pyrimidines.[6]

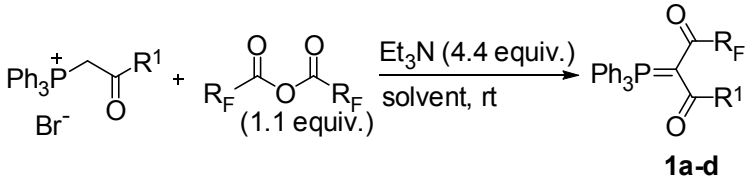
One of the most attractive methods for the construction of these heterocyles is based on the use of easily available fluorine-containing building blocks.[2] Fluorinated β-diketo phosphorus ylides (**1**), α-acyl-α-perfluoroacylmethylenetriphenylphosphorane, have been so far scarcely studied,[7] despite the fact that the ylides (**1**) should also be of interest as a novel synthone for CF_3-heterocycles due to the ready accessibility and the easy-to-handle compounds. Thus, the reactions of $Ph_3P{=}C(COCF_3)COPh$ (**1a**) and the related compounds with lithium reagents lead to the formation of fluorinated α,β-unsaturated ketones.[7a] Pyrolysis of **1a** gives acetylenic ketones.[7b]

Owing to the increasing importance of trifluoromethyl-containing heterocycles in biology, pharmacology, and industrial applications,[2d] we decided to investigate their reactions of the ylides (**1**) with amidines in order to develop new syntheses of trifluoromethylated and perfluoroalkylated pyrimidines.

RESULTS AND DISCUSSION

The differently fluorinated compounds **1a-d**, known compounds, were easily prepared in moderate to good yields by the reaction of acyl ylides with perfluorinated anhydrides (Table 1).[7]

Table 1. Preparations of ylides (**1a-d**)

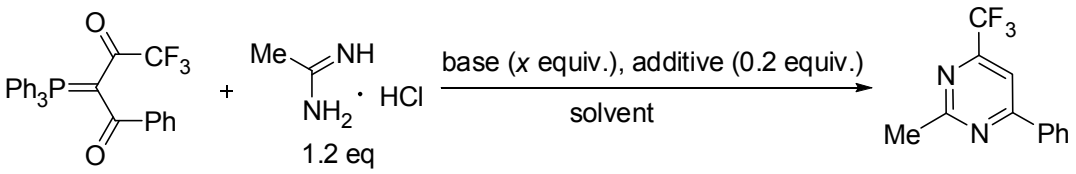


1a-d

Entry	R_F	R^1	Solvent	Time (h)	Yields (%)
1	CF_3	Ph	THF	1	**1a** (81)
2	CF_3	Me	MeCN	24	**1b** (73)
3	C_2F_5	Ph	THF	24	**1c** (46)
4	C_3F_7	Ph	THF	24	**1d** (46)

As listed in Table 2, **1a** and acetamidine hydrochloride were used as the model substrates to optimize reaction conditions including the temperature, solvents, bases, and catalysts under argon atmosphere.

Table 2. Optimization of reaction conditions



1a **2a**

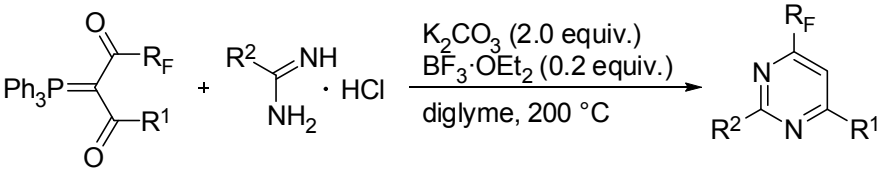
Entry	Base (*x* equiv.)	Additive	Solvent	Temp (°C)	Time (h)	Yields of **2a** (%)
1	Cs_2CO_3 (3)	CuBr	DMSO	80	5	NR[a]
2	Cs_2CO_3 (3)	CuBr	DMSO	150	5	20
3	Cs_2CO_3 (3)	CuBr	DMSO	200	1	23
4	Cs_2CO_3 (3)	CuBr	xylene	200	1	37
5	Cs_2CO_3 (3)	CuBr	diglyme	200	1	47
6	K_2CO_3 (2)	CuBr	diglyme	200	1	48
7	K_2CO_3 (2)	$ZnBr_2$	diglyme	200	1	58
8	K_2CO_3 (2)	$ZnBr_2$	DMF	150	5	47
9	AcONa (3)	$ZnBr_2$	DMF	150	9	14
10	DBU (3)	$ZnBr_2$	diglyme	200	1	NR[a]
11	Cs_2CO_3 (3)	-	DMSO	150	5	17
12	K_2CO_3 (2)	-	diglyme	200	1	18
13	K_2CO_3 (2)	$ZnCl_2$	diglyme	200	1	60
14	K_2CO_3 (2)	ZnI_2	diglyme	200	1	61
15	K_2CO_3 (2)	$Zn(OAc)_2$	diglyme	200	1	63
16	K_2CO_3 (2)	$CuBr_2$	diglyme	200	1	49
17	K_2CO_3 (2)	CuCl	diglyme	200	1	47
18	K_2CO_3 (2)	CuI	diglyme	200	1	58
19	K_2CO_3 (2)	Cu_2O	diglyme	200	1	41
20	K_2CO_3 (2)	CuOTf·PhH	diglyme	200	1	56
21	K_2CO_3 (2)	$Cu(OTf)_2$	diglyme	200	1	53
22	K_2CO_3 (2)	$Cu(OAc)_2 \cdot H_2O$	diglyme	200	1	51
23	K_2CO_3 (2)	$MgBr_2$	diglyme	200	1	56
24	K_2CO_3 (2)	MgI_2	diglyme	200	1	62
25	K_2CO_3 (2)	LiCl	diglyme	200	1	57
26	K_2CO_3 (2)	$TiCl_4$	diglyme	200	1	43
27	K_2CO_3 (2)	$AlCl_3$	diglyme	200	1	56
28	K_2CO_3 (2)	$CeCl_3$	diglyme	200	1	67
29	K_2CO_3 (2)	$FeCl_3$	diglyme	200	1	66
30	K_2CO_3 (2)	$Yb(OTf)_3$	diglyme	200	1	62
31	K_2CO_3 (2)	$Sc(OTf)_3$	diglyme	200	1	56
32	K_2CO_3 (2)	$BF_3 \cdot OEt_2$	diglyme	200	1	69

[a] no reaction

At first, the effects of temperature were investigated in the presence of 3 equiv of Cs_2CO_3 and 0.2 equiv of CuBr (entries 1-5). The temperature strongly influenced the yield. High temperature (200 °C) was needed to obtain a good yield of **2a** (entry 5). Various solvents such as DMSO, xylene, and diglyme were tested (entries 3-5), the last one is the solvent of choice for the reaction (entry 5). Instead of Cs_2CO_3 (entry 5), K_2CO_3 also gave the good result (entry 6). When the reaction was performed in the presence of $ZnBr_2$ instead of CuBr, **2a** was obtained in a good yield (58%) (entry 7). Among various bases such as K_2CO_3, AcONa, and DBU (entry 7-10), K_2CO_3 gave best results in the presence of $ZnBr_2$ (entry 7). No pyrimidine was detected when organic base such as DBU was used (entry 10). The product **2a** was obtained in low yield or not at all in the absence of additives such as CuBr and $ZnBr_2$ (entries 11 and 12). To further improve the yield, we have extensively screened various additives (entries 13-32) in the presence of two equiv of K_2CO_3 and found that BF_3 etherate was the best additive. We conducted that the most efficient set of conditions employs 1.0 equiv of **1a**, 1.2 equiv of acetamidine hydrochloride, 2 equiv of K_2CO_3 and 0.2 equiv of BF_3 etherate in diglyme at 200 °C (entry 32).

Next, the scope of the procedure with respect to other substrates was studied (Table 3). Under these conditions, product **2b** was obtained in 98% yield by treating **1a** with benzamidine (entry 2). The reaction with *O*-methylisourea afforded 2-methoxy- (**2eA**) and 2-hydroxypyrimidine (**2eB**) in low yields, respectively (entry 5). 4-Pentafluoroethyl- (**2g**) and 4-heptafluoro-*n*-propylpyrimidine (**2h**) were obtained in high yields, respectively (entries 7 and 8).

Table 3. Reactions with various amidines



1a-d **2a-h**

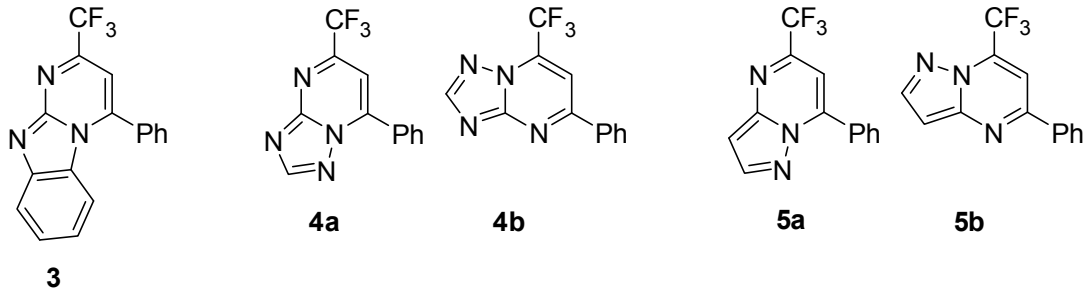
Entry	**1**	R_F	R^1	R^2	Time (h)	Yields of **2** (%)
1	**a**	CF_3	Ph	Me	1	**2a** (69)
2	**a**	CF_3	Ph	Ph	1	**2b** (98)
3	**a**	CF_3	Ph	H	1	**2c** (51)
4	**a**	CF_3	Ph	NH_2	1	**2d** (56)
5[a]	**a**	CF_3	Ph	OMe	1	**2eA** (21) [b]
6	**b**	CF_3	Me	Ph	6	**2f** (84)
7	**c**	C_2F_5	Ph	Ph	1	**2g** (91)
8	**d**	C_3F_7	Ph	Ph	1	**2h** (83)

[a] Methylisourea was used as a H_2SO_4 salt .
[b] Plus **2eB** (R^2=OH, 18% yield)

These reaction conditions are also suitable for cyclocondensation of **1a** with cyclic amidines such as 2-aminobenzimidazole, 3-amino-1,2,4-triazole, and 3-aminopyrazole (Scheme 1). The reaction of **1a** with 2-aminobenzimidazole gave 4-phenyl-2-(trifluoromethyl)pyrimido[1,2-*a*]benzimidazole (**3**) in 66% yield. The compound **3** has been previously prepared as one of the two regioisomers from the reaction between 1,1,1-trifluoro-4-methoxy-4-phenylbut-3-en-2-one and 2-aminobenzimidazole.[8]

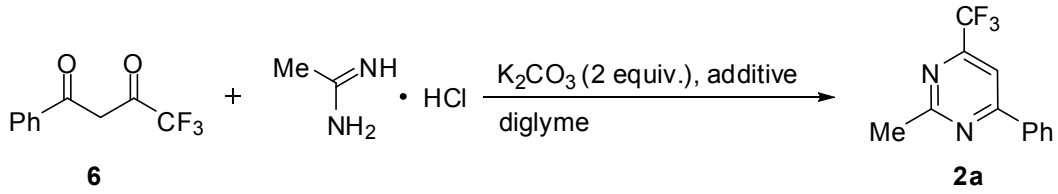
The reaction of **1a** with 3-amino-1,2,4-triazole gave a mixture of **4a** and **4b** (2:3) in 56% yield, in which the authentic **4b** was prepared by the condensation of 4-ethoxy-1,1,1-trifluoro-4-phenylbut-3-en-2-one and 3-amino-1,2,4-triazole.[9]

The reaction of **1a** with 3-aminopyrazole gave a mixture of **5a** and **5b** (1:1) in 75% yield. The authentic **5a** was alternatively prepared by the condensation of 4,4,4-trifluoro-1-phenylbutane-1,3-dione (**6**) and 3-aminopyrazole.[10]



Scheme 1

Table 4. Reactions of 1-phenyl-4,4,4-trifluorobutan-1,3-dione (**6**) with acetamidine



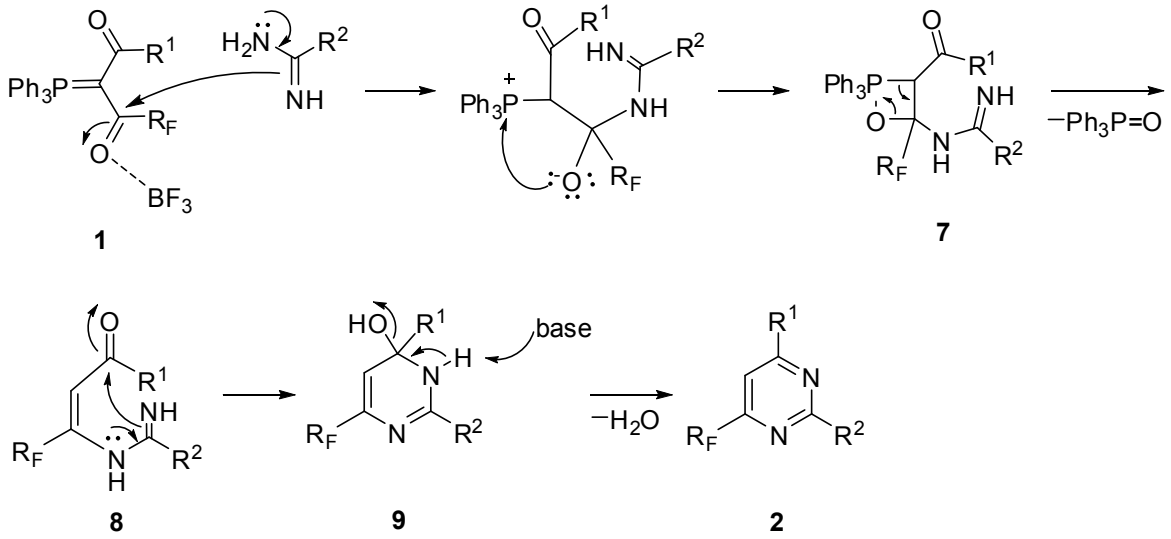
Entry	Acetamidine HCl (equiv.)	Base (equiv.)	Additive (equiv.)	Solvent	Temp (°C)	Time (h)	Yields of **2a**
1	2.3	NaOMe (1.0)	-	MeOH	80	30	NR[a]
2	1.0	KOH (1.1)	-	MeOH	80	22	NR[a]
3	1.0	NaOAc (1.0)	-	DMF	80	24	NR[a]
4	1.2	K_2CO_3 (2.0)	-	EtOH	100	12	NR[a]
5	1.2	K_2CO_3 (2.0)	$BF_3{\cdot}OEt_2$ (0.2)	diglyme	200	1	3.2

[a] no reaction

Finally, we examined the reactions of **6** with acetamidine. Because reactions of **6** and amidines such as guanidine derivatives, *S*-methylisothiourea, and 5-aminopyrazoles have been reported to afford the corresponding trifluoromethylpyrimidines.[4a] However, the reactions with other amidines such as

acetamidine and benzamidine were not reported. According to our observations, no reaction occurred when acetamidine was heated under several reaction conditions with **6** (Table 4, entries 1-4). The product **2a** was obtained in only 3.2% yield (entry 5), when the reaction was performed under the same conditions with **1a** (Table 3, entry 1). In contrast, our results with **1a** indicate the clear advantage of using **1** (Table 3).

All the pyrimidines prepared were characterized by ^{13}C and ^{1}H NMR spectroscopy and mass spectrometry. Products **2a**,[11] **2b**,[4b] **2d**,[11] **2eA**,[12] **2eB**,[13] **2h**,[14] **3**,[8] **4b**,[9] and **5a**[10] have been described and characterized previously, while compounds **2c**, **2eB**, **2f**,[15] **2g**, **4a**, and **5b** have not been characterized, or are unknown compounds.



Scheme 2

Being two electrophilic centers in 1,3-positions, trifluoromethyl β-diketo phosphorus ylides (**1**) can be undergo cyclization reactions with 1,3-binucleophilic agents of amidines to pyrimidines **2**. There have been reports that these unsymmetrical 1,3-diketones react with water, alcohols, ethanethiol, pyrrolidine and hydrazines to give the adducts at the $COCF_3$ carbonyl.[16] It is therefore likely that the reaction proceeds *via* addition of amidines to the $COCF_3$ carbonyl activated by the Lewis acidic BF_3, as shown in Scheme 2. The intermediate oxaphophetane **7** undergoes elimination of triphenylphosphine oxide to give **8**. Subsequent intramolecular cyclization of **7** affords dihydropyrimidine **9**. One molecule of water is then eliminated to give the aromatic pyrimidines **2**.

In conclusion, we examined the scope and limitation of the cyclocondensation of fluorinated β-diketo phosphorus ylides **1** with amidines. The reaction was applicable to a wide range of amidines possessing various substituents to give 2,6-disubstituted 4-trifluoromethylpyrimidines in good yields. Moreover,

the method appears to be useful and convenient for construction of 4-perfluoroalkylpyrimidines in terms of the ready accessibility of the starting materials, cheap reagents, and operational simplicity.

EXPERIMENTAL

All melting points were determined using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on Bruker AVANCE500 spectrometer with tetramethylsilane (Me_4Si) as an internal reference. ^{13}C-NMR spectra were obtained on a Bruker AVANCE500 spectrometer (at 126 MHz). Both ^{1}H- and ^{13}C-NMR spectral data are reported in parts per million (δ) relative to Me_4Si. ^{31}P-NMR spectra were obtained on a Bruker AVANCE500 spectrometer (at 202 MHz) and were reported relative to external standard 85% aqueous phosphoric acid. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrometer. Low- and high-resolution MS were obtained with a JEOL JMS-GC mate II spectrometer with a direct inlet system at 70 eV and a Bruker micrOTOF-Q mass spectrometer with methanol as the solvent. Elemental analyses were carried out on a Yanaco CHN Corder MT-5 at the Integrated Center for Science, Ehime University. Standard work-up means that the organic layers were finally dried over Na_2SO_4, filtered, and concentrated *in vacuo* below 45 °C using a rotary evaporator.

General procedure for the preparation of α-acyl-α-perfluoroacylmethylenetriphenylphosphoranes (1): These compounds were prepared by employing the reported method[17] with slight modifications. To a suspension of a phosphonium salt (11.0 mmol) in THF (25 mL) was added triethylamine (48.4 mmol) at 0 °C, and the mixture was stirred for 30 min. To the mixture was added dropwise perfluorinated anhydride (12.1 mmol), and the whole was stirred at rt for indicated time in Table 1. The precipitate was filtered off, washed with cold THF (x 3), and the filtrate was evaporated. The residue was triturated with water, and the insoluble material was collected by filtration, washed with water, and dried in vacuo to give the product **1**.

4,4,4-Trifluoro-1-phenyl-2-(triphenylphosphoranylidene)butane-1,3-dione (1a). Yellow crystals, 81% yield. mp 179–181 °C (MeOH) (mp[18] 182–183 °C). IR (KBr): 3063, 2357, 1643, 1577, 1561, 1440, 1264, 1200, 1169, 1131, 1108, 886, 750, 688, 507 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36 (t, *J* = 7.5 Hz, 2H, Ar*H*), 7.47 (td, *J* = 7.8, 3.2 Hz, 7H, Ar*H*), 7.57 (t, *J* = 7.4 Hz, 3H, Ar*H*), 7.66 (d, *J* = 12.9 Hz, 3H, Ar*H*), 7.68 (d, *J* = 13.0 Hz, 3H, Ar*H*), 7.83 (d, *J* = 8.1 Hz, 2H, Ar*H*) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 20.93 ppm. MS (EI) *m/z*: 476 (M^+, 26), 129 (100).

1,1,1-Trifluoro-3-(triphenylphosphoranylidene)pentane-2,4-dione (1b).[18] The solvent was MeCN instead of THF. Pale yellow crystals, 73% yield. mp 138–140 °C ($CHCl_3$/hexane). IR (KBr): 3465, 3058, 2921, 2363, 1580, 1561, 1484, 1441, 1273, 1192, 1178, 1133, 1106, 942, 755, 748, 688, 512 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.34 (s, 3H, C*H*$_3$), 7.47 (td, *J* = 7.9, 3.2 Hz, 6H, Ar*H*), 7.56 (tq, *J* = 7.5,

2.0 Hz, 3H, Ar*H*), 7.64 (dd, *J* = 13.0, 1.4 Hz, 3H, Ar*H*), 7.65 (d, *J* = 13.0 Hz, 3H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 30.2 (dq, $^3J_{C\text{-}P}$ = 5.5 Hz, $^5J_{C\text{-}F}$ = 4.5 Hz, *C*H_3), 85.4 (d, $^1J_{C\text{-}P}$ = 106.8 Hz, *C*=P), 117.7 (qd, $^1J_{C\text{-}F}$ = 290.6 Hz, $^3J_{C\text{-}P}$ = 15.9 Hz, *C*F_3), 124.8 (d, $^1J_{C\text{-}P}$ = 93.1 Hz, *Ar*), 128.9 (d, $^2J_{C\text{-}P}$ = 12.7 Hz, *Ar*), 132.2 (d, $^4J_{C\text{-}P}$ = 2.8 Hz, *Ar*), 133.1 (d, $^3J_{C\text{-}P}$ = 10.0 Hz, *Ar*), 174.6 (qd, $^2J_{C\text{-}F}$ = 34.0 Hz, $^2J_{C\text{-}P}$ = 8.8 Hz, *C*OCF_3), 194.2 (d, $^2J_{C\text{-}P}$ = 4.2 Hz, *C*OCH_3) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 19.83 ppm. MS (EI) *m/z*: 414 (M^+, 43), 345 (100).

4,4,5,5,5-Pentafluoro-1-phenyl-2-(triphenylphosphoranylidene)pentane-1,3-dione (1c).[19] Yellow crystals, 46% yield. mp 171–173 °C (MeOH). IR (KBr): 3070, 1640, 1556, 1439, 1325, 1251, 1216, 1169, 1108, 1018, 881, 778, 748, 728, 716, 691, 518 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.36 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.46 (td, *J* = 7.9, 3.2 Hz, 7H, Ar*H*), 7.57 (td, *J* = 7.5, 1.9 Hz, 3H, Ar*H*), 7.64 (dd, *J* = 13.0, 1.3 Hz, 3H, Ar*H*), 7.65 (d, *J* = 13.2 Hz, 3H, Ar*H*), 7.87 (dd, *J* = 8.3, 1.4 Hz, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 81.3 (d, $^1J_{C\text{-}P}$ = 99.2 Hz, *C*=P), 108.7 (tqd, $^1J_{C\text{-}F}$ = 269.1 Hz, $^2J_{C\text{-}F}$ = 36.7 Hz, $^3J_{C\text{-}P}$ = 12.6 Hz, *C*F_2), 118.8 (qt, $^1J_{C\text{-}F}$ = 289.3 Hz, $^2J_{C\text{-}F}$ = 35.7 Hz, *C*F_3), 123.8 (d, $^1J_{C\text{-}P}$ = 92.6 Hz, *Ar*), 128.1, 129.0 (d, $^2J_{C\text{-}P}$ = 12.7 Hz, *Ar*), 129.3, 132.0, 132.6 (d, $^4J_{C\text{-}P}$ = 3.7 Hz, *Ar*), 133.6 (d, $^3J_{C\text{-}P}$ = 10.3 Hz, *Ar*), 142.2 (dt, $^3J_{C\text{-}P}$ = 5.5 Hz, $^5J_{C\text{-}F}$ = 2.8 Hz, *Ar*), 174.5 (td, $^2J_{C\text{-}F}$ = 24.6 Hz, $^2J_{C\text{-}P}$ = 5.3 Hz, *C*OCF_3), 192.1 (d, $^2J_{C\text{-}P}$ = 7.3 Hz, *C*OPh) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 21.08 ppm. MS (ESI) *m/z*: 527 $[M+H]^+$. *Anal*. Calcd for $C_{29}H_{20}F_5O_2P$: C, 66.16; H, 3.83. Found: C, 65.99; H, 3.60; N, 0.17.

4,4,5,5,6,6,6-Heptafluoro-1-phenyl-2-(triphenylphosphoranylidene)hexane-1,3-dione (1d). Yellow crystals, 46% yield. mp 147–149 °C (MeOH) (mp[7b] 143 °C). IR (KBr): 3085, 3066, 1652, 1577, 1557, 1439, 1335, 1259, 1223, 1208, 1111, 928, 885, 752, 716, 693, 517 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.35 (t, *J* = 7.9 Hz, 2H, Ar*H*), 7.45 (td, *J* = 7.9, 3.0 Hz, 7H, Ar*H*),7.56 (td, *J* = 7.6, 1.9 Hz, 3H, Ar*H*), 7.63 (dd, *J* = 13.0, 1.4 Hz, 3H, Ar*H*), 7.65 (d, *J* = 12.9 Hz, 3H, Ar*H*), 7.86 (dd, *J* = 8.5, 1.5 Hz, 2H, Ar*H*) ppm. ^{31}P NMR (202 MHz, $CDCl_3$) δ = 20.88 ppm. MS (EI) *m/z*: 576 (M^+, 22), 407 (100).

General Procedure for Reaction of Fluorinated β-diketo phosphorus ylides with various amidines (2): To a stirred suspension of **1** (0.5 mmol), amidine (0.6 mmol), and K_2CO_3 (158 mg, 1.0 mmol) in diglyme (2.5 mL) was added $BF_3{\cdot}OEt_2$ (13 μL, 0.1 mmol), and the mixture was heated at 200 °C for 1 h. After cooling to rt, and work up with 5% aq NaOH (30 mL), the mixture was extracted with AcOEt (30 mL x 3). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane:AcOEt = 18:1 to 2:1) to give **2**.

2-Methyl-6-phenyl-4-(trifluoromethyl)pyrimidine (2a).[11] Yellow oil, 82 mg, 69% yield. IR (neat): 3067, 1594, 1554, 1388, 1260, 1142, 879, 832, 765, 716, 693, 641, 450 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.89 (s, 3H, C*H*$_3$), 7.52–7.58 (m, 3H, Ar*H*), 7.83 (s, 1H, *H*-5), 8.14 (dd, *J* = 7.8, 2.0 Hz, 2H, Ar*H*) ppm. MS (EI) *m/z*: 238 (M^+, 100).

2,6-Diphenyl-4-(trifluoromethyl)pyrimidine (2b). White crystals, 147 mg, 98% yield. mp 77–79 °C (MeOH/H_2O) (mp[4b] 83–84 °C). IR (KBr): 3067, 2972, 2927, 1591, 1460, 1380, 1286, 1166, 1028, 874, 848, 831, 778, 757, 715, 658, 633 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.53–7.59 (m, 6H, Ar*H*), 7.90 (s, 1H, *H*-5), 8.27–8.28 (m, 2H, Ar*H*), 8.63–8.65 (m, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 109.9 (q, $^3J_{C\text{-}F}$ = 2.8 Hz, *C*-5), 120.9 (q, $^1J_{C\text{-}F}$ = 275.8 Hz, *C*F_3), 127.5, 128.7, 128.7, 129.2, 131.6, 131.9, 136.0, 136.6, 156.8 (q, $^2J_{C\text{-}F}$ = 35.8 Hz, *C*-4), 165.4, 166.5 ppm. MS (EI) *m/z*: 300 (M^+, 100).

6-Phenyl-4-(trifluoromethyl)pyrimidine (2c). Yellow crystals, 57 mg, 51% yield. mp 31–33 °C (hexane). IR (KBr): 3077, 1598, 1393, 1305, 1263, 1200, 1172, 1143, 1062, 890, 766, 694, 634 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 7.53–7.60 (m, 3H, Ar*H*), 8.03 (s, 1H, *H*-5), 8.16 (dd, *J* = 7.6, 1.6 Hz, 2H, Ar*H*), 9.39 (s, 1H, *H*-2) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 112.5 (q, $^3J_{C\text{-}F}$ = 2.6 Hz, *C*-5), 120.7 (q, $^1J_{C\text{-}F}$ = 275.7 Hz, *C*F_3), 127.4, 129.3, 132.1, 135.4 156.2 (q, $^2J_{C\text{-}F}$ = 35.8 Hz, *C*-4), 159.4, 166.5 ppm. MS (EI) *m/z*: 224 (M^+, 13), 128 (100). HRMS (ESI) for $C_{11}H_8F_3N_2$ $[M+H]^+$: Calcd, 225.0634. Found, 225.0630.

6-Phenyl-4-(trifluoromethyl)pyrimidin-2-amine (2d). White crystals, 67 mg, 56% yield. mp 128–129 °C (MeOH/H_2O) (mp[11] 130–132 °C). IR (KBr): 3495, 3320, 3210, 1636, 1598, 1556, 1458, 1386, 1263, 1242, 1193, 1180, 1126, 997, 835, 773, 688, 648, 435 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.35 (br s, 2H, NH_2), 7.35 (s, 1H, *H*-5), 7.48–7.53 (m, 3H, Ar*H*), 8.04 (dd, *J* = 7.9, 1.8 Hz, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 102.9 (q, $^3J_{C\text{-}F}$ = 2.9 Hz, *C*-5), 120.8 (q, $^1J_{C\text{-}F}$ = 275.7 Hz, *C*F_3), 127.3, 129.0, 131.5, 136.2, 157.2 (q, $^2J_{C\text{-}F}$ = 35.3 Hz, *C*-4), 163.5, 168.2 ppm. MS (EI) *m/z*: 239 (M^+, 100).

2-Methoxy-6-phenyl-4-(trifluoromethyl)pyrimidine (2eA). Yellow crystals, 27 mg, 21% yield. mp 39–40 °C (hexane) (mp[12] 47–48 °C). IR (KBr): 3003, 2962, 2928, 1601, 1551, 1480, 1396, 1362, 1258, 1196, 1148, 1042, 913, 869, 779, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 4.16 (s, 3H, OCH_3), 7.51–7.59 (m, 3H, Ar*H*), 7.68 (s, 1H, *H*-5), 8.15 (dd, *J* = 8.0, 1.7 Hz, 2H, Ar*H*) ppm. MS (EI) *m/z*: 254 (M^+, 100).

2-Hydroxy-6-phenyl-4-(trifluoromethyl)pyrimidine (2eB). White crystals, 22 mg, 18% yield. mp 230–232 °C ($CHCl_3$/hexane) (mp[13] 233–235 °C). IR (KBr): 3504, 3149, 3077, 2972, 1661, 1613, 1578, 1561, 1397, 1265, 1200, 1149, 1107, 1005, 773, 689 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ = 7.49–7.58 (m, 3H, Ar*H*), 7.73 (br s, 1H, *H*-5), 8.13 (d, *J* = 7.5 Hz, 2H, Ar*H*), 12.8 (br s, 1H, O*H*) ppm. ^{13}C NMR (126 MHz, DMSO-d_6) δ = 103.1, 120.4 (q, $^1J_{C\text{-}F}$ = 276.2 Hz, *C*F_3), 127.6, 129.0, 132.2, 133.9, 157.9, 163.7, 167.3 ppm. MS (EI) *m/z*: 240 (M^+, 100).

6-Methyl-2-phenyl-4-(trifluoromethyl)pyrmidine (2f).[15] Yellow crystals, 100 mg, 84% yield. mp 54–56 °C (hexane). IR (KBr): 3042, 1597, 1401, 1375, 1243, 1186, 1143, 859, 763, 714, 968, 554 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ = 2.70 (s, 3H, CH_3), 7.36 (s, 1H, *H*-5), 7.48–7.52 (m, 3H, Ar*H*), 8.50–8.52

(m, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 24.7, 113.9 (q, $^3J_{C-F}$ = 2.5 Hz), 120.8 (q, $^1J_{C-F}$ = 275.6 Hz, *C*F_3), 128.6, 131.4, 136.5, 155.7 (q, $^2J_{C-F}$ = 35.5 Hz), 165.1, 170.1 ppm. MS (ESI) *m/z*: 239 $[M+H]^+$. *Anal*. Calcd for $C_{12}H_9F_3N_2$: C, 60.51; H, 3.81; N, 11.76. Found: C, 60.62; H, 4.11; N, 11.56.

2,6-Diphenyl-4-(pentafluoroethyl)pyrimidine (2g). White crystals, 159 mg, 91% yield. mp 81–82 °C (MeOH). IR (KBr): 3076, 1587, 1575, 1545, 1384, 1371, 1332, 1212, 1198, 1164, 1152, 1009, 757, 735, 692 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.52–7.56 (m, 6H, Ar*H*), 7.91 (s, 1H, *H*-5), 8.24–8.26 (m, 2H, Ar*H*), 8.61–8.63 (m, 2H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 110.8 (tq, $^1J_{C-F}$ = 255.7 Hz, $^2J_{C-F}$ = 38.2 Hz, *C*F_2), 111.3 (t, $^3J_{C-F}$ = 3.9 Hz, *C*-5), 118.8 (qt, $^1J_{C-F}$ = 287.3 Hz, $^2J_{C-F}$ = 36.4 Hz, *C*F_3), 127.5, 128.7, 128.8, 129.2, 131.6, 131.9, 136.0, 136.6, 156.8 (t, $^2J_{C-F}$ = 26.0 Hz, *C*-4), 165.1, 166.3 ppm. MS (ESI) *m/z*: 373 $[M+Na]^+$. *Anal*. Calcd for $C_{18}H_{11}F_5N_2$: C, 61.72; H, 3.17; N, 8.00. Found: C, 61.83; H, 3.18; N, 7.87.

2,6-Diphenyl-4-(heptafluoropropyl)pyrmidine (2h). White crystals, 166 mg, 83% yield. mp 66–67 °C (MeOH) (mp[14] 85–86 °C). IR (KBr): 3067, 2980, 1589, 1574, 1547, 1374, 1342, 1230, 1207, 1196, 1185, 1114, 929, 735, 687 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.53–7.59 (m, 6H, Ar*H*), 7.91 (s, 1H, *H*-5), 8.27–8.29 (m, 2H, Ar*H*), 8.62–8.64 (m, 2H, Ar*H*) ppm. MS (EI) *m/z*: 400 (M^+, 68), 128 (100).

4-Phenyl-2-(trifluoromethyl)pyrimido[1,2-*a*]benzimidazole (3). Yellow crystals, 103 mg, 66% yield. mp 190–192 °C (MeOH/H_2O) (mp[8] 188 °C). IR (KBr): 3077, 3049, 3033, 1532, 1493, 1452, 1443, 1401, 1261, 1189, 1177, 1144, 1110, 1091, 831, 769, 740, 707, 702 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.79 (d, *J* = 8.6 Hz, 1H, Ar*H*), 7.07 (s, 1H, Ar*H*), 7.14 (t, *J* = 7.5 Hz, 1H, Ar*H*), 7.55 (t, *J* = 7,5 Hz, 1H, Ar*H*), 7.63 (d, *J* = 7.2 Hz, 2H, Ar*H*), 7.70 (t, *J* = 7.8 Hz, 2H, Ar*H*), 7.76 (t, *J* = 7.4 Hz, 1H, Ar*H*), 8.07 (d, *J* = 8.3 Hz, 1H, Ar*H*) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ = 103.4 (q, $^3J_{C-F}$ = 1.6 Hz, *C*-3), 115.1, 120.4 (q, $^1J_{C-F}$ = 276.6 Hz, CF_3), 121.1, 122.6, 127.0, 128.1, 129.7, 131.5, 131.8, 145.7, 149.8, 151.7 (q, $^2J_{C-F}$ = 36.9 Hz), 151.9 ppm. MS (EI) *m/z*: 313 (M^+, 100).

Mixture of 7-Phenyl-5-(trifluoromethyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (4a) and 5-Phenyl-7-(trifluoromethyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (4b). Pale yellow crystals, 296 mg, 56% yield (from 2.0 mmol scale of **1a**, **4a**:**4b** = 2:3). mp 135–139 °C (**4b**: mp[9] 143–146 °C). IR (KBr): 3080, 1547, 1455, 1400, 1295, 1265, 1218, 1183, 1146, 987, 852, 771, 698, 625 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) **4a**: δ = 7.57 (s, 1H, *H*-6), 7.64–7.70 (m, 3H, Ar*H*), 8.18 (dd, *J* = 8.0, 1.6 Hz, 2H, Ar*H*), 8.72 (s, 1H, *H*-2) ppm. **4b**: δ = 7.57–7.63 (m, 3H, Ar*H*), 7.90 (s, 1H, *H*-6), 8.25 (dd, *J* = 7.8, 1.9 Hz, 2H, Ar*H*), 8.64 (s, 1H, *H*-2) ppm. MS (EI) *m/z*: 264 (M^+, 16.8), 83 (100).

Mixture of 7-Phenyl-5-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (5a) and 5-Phenyl-7-(trifluoromethyl)pyrazolo[1,5-*a*]pyrimidine (5b). Yellow crystals, 99 mg, 75% yield (**5a**:**5b** = 1:1). mp 58–62 °C (**5a**: mp[10] 100 °C). IR (KBr): 3133, 3104, 3063, 1633, 1558, 1397, 1344, 1337, 1286,

1277, 1261, 1230, 1195, 1162, 1141, 861, 770, 691, 624 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) **5a**: δ = 6.98 (d, *J* = 2.4 Hz, 1H, *H*-3), 7.22 (s, 1H, *H*-6), 7.59–7.63 (m, 3H, Ar*H*), 8.10–8.12 (m, 2H, Ar*H*), 8.31 (d, *J* = 2.3 Hz, 1H, *H*-2) ppm. **5b**: δ = 6.86 (d, *J* = 2.5 Hz, 1H, *H*-3), 7.50–7.53 (m, 3H, Ar*H*), 7.60 (s, 1H, *H*-6), 8.08–8.10 (m, 2H, Ar*H*), 8.25 (d, *J* = 2.4 Hz, 1H, *H*-2) ppm. MS (EI) *m/z*: 263 (M^+, 100).

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