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Organo-catalyzed Michael addition of 2-fluoro-2-arylacetonitriles

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ABSTRACT

An efficient synthesis of a variety of 2-arylacetonitriles containing a fluorinated stereogenic center through organo-catalyzed Michael addition reaction of 2-fluoro-2-arylacetonitriles has been developed. This protocol uses a cheap organocatalyst (DBU) and has a broad substrate scope: α, β-unsaturated ketones, esters, nitriles and sulfones were all successfully reacted. Importantly, water proved to be a good solvent for this reaction.

The introduction of fluorine into organic molecules can often result in unique physical, chemical, and biological properties [1]. Not surprisingly, fluorine is highly valued in the synthetic and medicinal communities. Organic molecules that contain a fluorinated stereogenic center have attracted a lot of attention because they are present in many biologically active compounds and pharmaceuticals [2]. A large number of synthetic methods have been developed for the synthesis of such compounds bearing a fluorinated stereogenic center [1,2]. Among these, the 1,4-addition of monofluorinated carbanions to α, β-unsaturated Michael acceptors represents a straightforward and simple approach. Because a fluorinated carbanion is significantly destabilized by the electronic repulsion between the electron pairs on the small fluorine atom and the electron lone pair occupying the *p*-orbital of the carbanion [3], α-functionalization of monofluorinated nucleophiles with strong electron-withdrawing groups has commonly been used to overcome the problem. To date, many monofluorinated nucleophiles featuring two strong electron-withdrawing groups (such as nitro, cyano, sulfonyl and carbonyl group) at the germinal position to fluorine have been commonly used in the Michael addition [4]. However, the use of monofluorinated nucleophiles functionalized with only one electron-withdrawing group in the Michael addition reaction is still challenging. For example, the 1,4-addition of $PhSO_2CH_2F$ to chalcones using LHMDS at −78 °C gave a mixture of 1,2- and 1,4-adducts (Scheme 1a) [5]. α-Fluoroacetophenone has also been successfully used as a Michael donor in the Michael addition. However, the preactivation of α-fluoroacetophenone to form fluorinated *Z*- and *E*-enamines was required (Scheme 1b) [6]. Finally, nitro proved to be a good activating group, and the Michael addition of 2-fluoronitroalkanes to α, β-unsaturated carbonyl compounds, acrylonitrile and nitroalkenes has been reported using an organic base or $RuH_2(PPh_3)_4$ as a catalyst (Scheme 1c) [7].

The cyano is an important one-carbon functional group. It can undergo a multitude of transformations to produce synthetically important carboxylic acids, amides, amines, aldehydes, and ketones. Also, the cyano is a strong electron-withdrawing group and has been frequently used to stabilize a carbanion. Not surprisingly, the use of 2-fluoronitriles as fluorocarbon nucleophiles to produce fluorinated stereogenic centers has received considerable attention [8]. For example, an elegant catalytic asymmetric Mannich reaction of 2-fluoro-2-phenylacetonitrile with ketimines has been recently reported [9]. To the best of our knowledge, the use of 2-fluoro-2-arylacetonitriles in the Michael addition has not been disclosed. As a continuation of our own interest in the reactivity and application of fluorocarbon nucleophiles [10], we herein report the first general use of 2-fluoro-2-arylacetonitriles in the Michael addition reaction. This reaction uses 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) as a catalyst and has a broad substrate scope: α,β-unsaturated ketones, esters, nitriles, and sulfones are all suitable substrates (Scheme 1d). In addition, water proved to be a good solvent for this reaction.

Using 2-fluoro-2-phenylacetonitrile **1a** as the Michael donor and (*E*)-chalcone **2a** as the Michael acceptor, we carried out our study by the examination of several commercially available organic bases (Table 1). Using DMAP or DABCO as an organocatalyst and DMSO as the reaction solvent, no reaction occurred, with the starting materials completely recovered (entries 1–2). This

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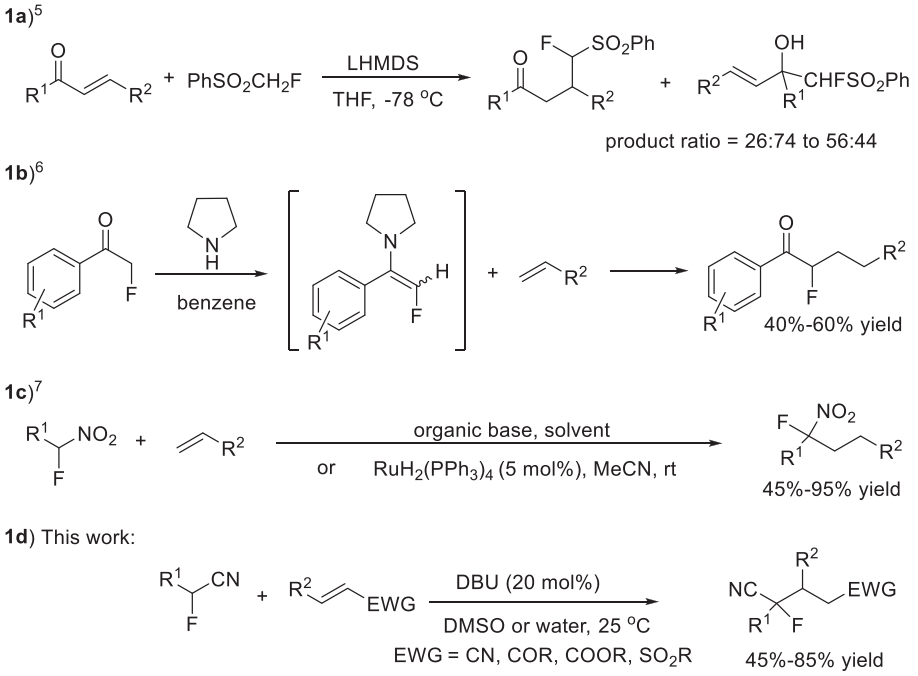
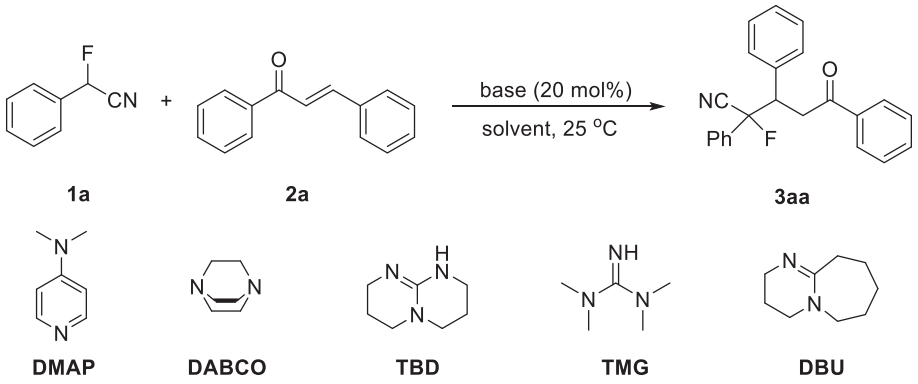


Scheme 1. The Michael addition of monofluorinated nucleophiles bearing an electron-withdrawing activating group.

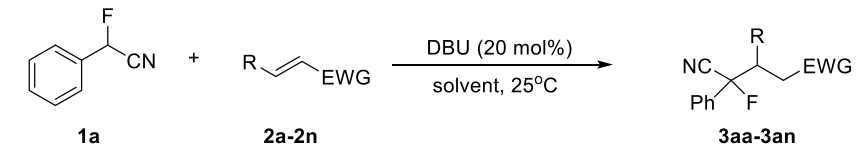
Table 1
Optimization of the Michael addition between 2-fluorophenylnitrile **1a** and chalcone **2a**.[a]



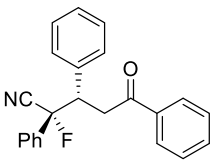
Entry	Base	Solvent	Time	Yield[d] (%)	d.r.[e]
1	DMAP	DMSO	24 h	0	–
2	DABCO	DMSO	24 h	0	–
3	K_2CO_3	DMSO	24 h	10	77:23
4	TBD	DMSO	45 min	95	70:30
5	TMG	DMSO	60 min	90	70:30
6	DBU	DMSO	25 min	97	71:29
7[b]	DBU	DMSO	3 h	82	72:28
8[c]	DBU	DMSO	60 min	95	72:28
9	DBU	Toluene	25 min	13	61:39
10	DBU	DMF	25 min	94	69:31
11	DBU	DCM	25 min	83	68:32
12	DBU	THF	25 min	95	69:31
13	DBU	MeCN	25 min	88	70:30
14	DBU	H_2O	25 min	97	70:30

[a] The reaction was perfomed with 0.45 mmol of **1a**, 0.45 mmol of **2a**, and 0.09 mmol of organocatalyst (20 mol %) in 3.0 mL solvent.
[b] 10 mol % DBU was used in the reaction, and other reaction conditions remain unchanged.
[c] The reaction was carried out at 5 °C.
[d] Isolated yield.
[e] d.r. was determined by ^{19}F NMR.

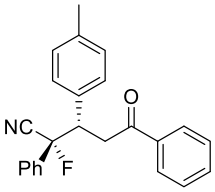
Table 2
Scope of the Michael addition of **1a** with respect to the Michael acceptor **2**.[a]



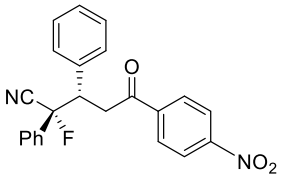
1a **2a-2n** **3aa-3an**



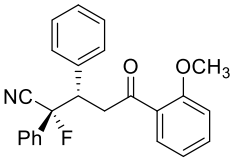
3aa
Condition A: 97%, 71:29 dr
Condition B: 97%, 70:30 dr



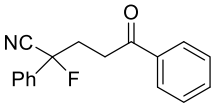
3ab
Condition A: 58%, 70:30 dr
Condition B: 61%, 60:40 dr



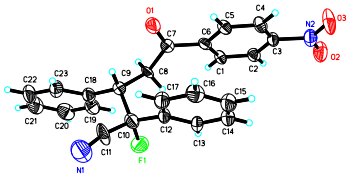
3ac
Condition A: 74%, 58:42 dr
Condition B: 50%, 74:26 dr

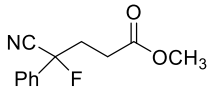


3ad
Condition A: 74%, 70:30 dr
Condition B: 72%, 60:40 dr

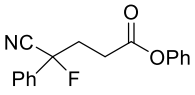


3ae
Condition A: 60%
Condition B: 55%

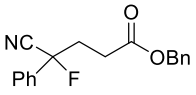




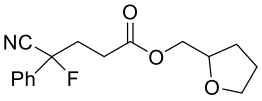
3af
Condition A: 85%
Condition B: 71%



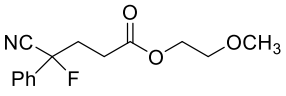
3ag
Condition A: 68%[b]
Condition B: 49%



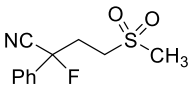
3ah
Condition A: 72%[b]
Condition B: 50%



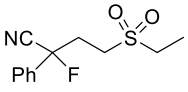
3ai
Condition A: 70%
Condition B: 46%



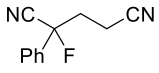
3aj
Condition A: 76%
Condition B: 52%



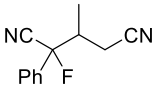
3ak
Condition A: 68%
Condition B: 77%



3al
Condition A: 78%[b]
Condition B: 61%



3am
Condition A: 80%
Condition B: 83%

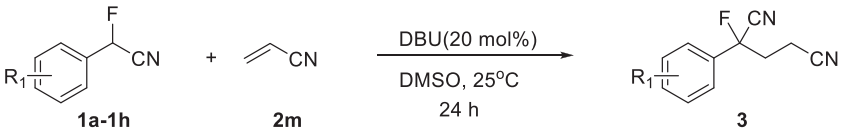


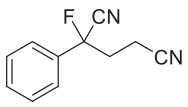
3an
Condition A: 65%, 67:33 dr
Condition B: 48%, 59:41 dr

[a]The reaction was performed with 0.45 mmol of **1a**, 0.45 mmol of **2a**, 20 mol % of catalyst and solvent (3.0 mL). Condition A: DMSO was used as the sole solvent. Condition B: water was used as the sole solvent.
[b]20 mol % of TMG was used as the base.

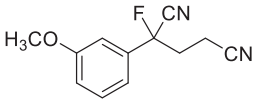
indicated that the strength of the bases used was not strong enough to deprotonate the α-H of **1a**. The use of inorganic base K_2CO_3 enabled the reaction to proceed, giving the desired product **3aa** in only 10% yield after a 24 h reaction (entry 3). Stronger bases including 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), 1,1,3,3-tetramethylguanidine (TMG) and DBU were found to be active (entries 4–6): in the presence of 20 mol % catalyst, the current transformation could be finished in 25–60 min and gave exclusively the Michael addition product **3aa** in an excellent yield (90–97% yield), albeit with a low diastereoselectivity (around 70:30). Further examination revealed that lowering the catalyst loading to 10 mol % resulted in a decrease of the yield (82%, entry 7). Using 20 mol % DBU, further screening of the reaction variables to improve the reaction was investigated. Lowering the reaction temperature to 5 °C gave a comparable diastereoselectivity, although the yield remained high (95%, entry 8). Evaluation of other solvents including toluene, DMF, DCM, THF and CH_3CN demonstrated no improvements with respect to both the yield and diastereoselectiv-

Table 3
Scope of the Michael addition reaction with respect to 2-fluoro-2-arylacetonitrile **1**.[a]

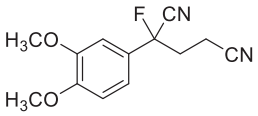




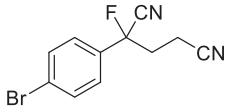
3am
Condition A: 80%
Condition B: 83%



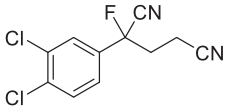
3bm
Condition A: 60%
Condition B: 35%



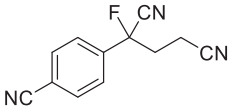
3cm
Condition A: 65%
Condition B: 45%



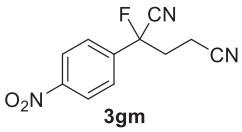
3dm
Condition A: 82%
Condition B: 79%



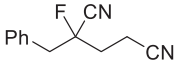
3em
Condition A: 94%
Condition B: 86%



3fm
Condition A: 80%
Condition B: 51%

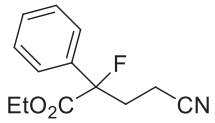


3gm
Condition A: 67%
Condition B: 58%

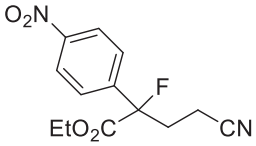


3hm
Condition A: 0%
Condition B: 0%

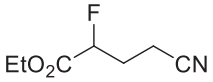
[a] The reaction was performed with 0.45 mmol of **1a**, 0.45 mmol of **2a**, 20 mol % of catalyst and solvent (3.0 mL). Condition A: DMSO was used as the sole solvent. Condition B: water was used as the sole solvent.



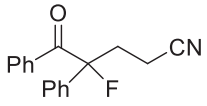
3im
Condition A: 62%
Condition B: 0%



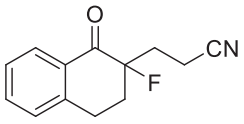
3jm
Condition A: 40%
Condition B: 51%



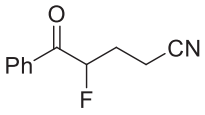
3mm
Condition A: 0%
Condition B: 0%



3km
Condition A: 72%
Condition B: 59%



3lm
Condition A: 74%
Condition B: 74%

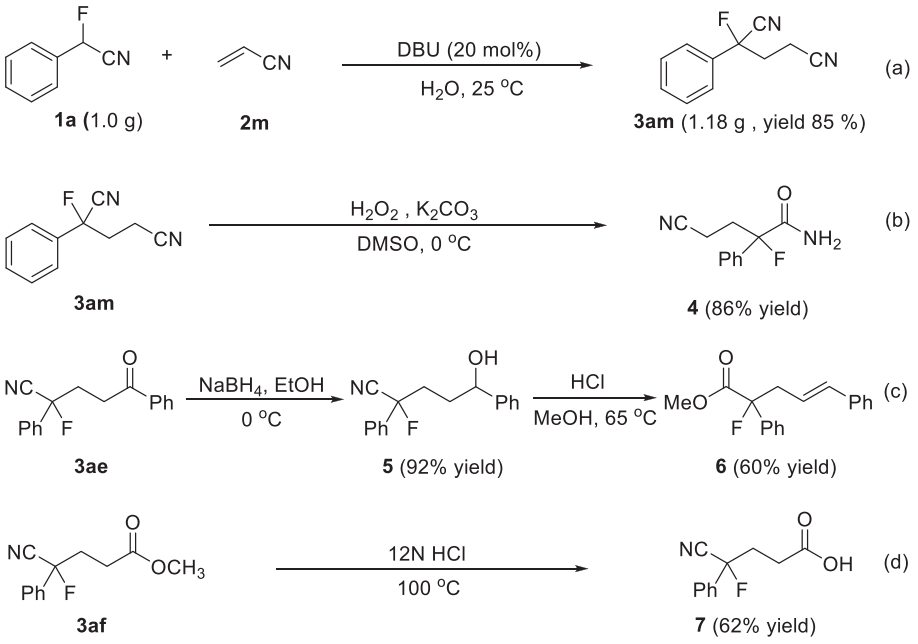


3nm
Condition A: 0%
Condition B: 0%

Scheme 2. The Michael reaction of α-fluorocarboxylates and α-fluoroketones with acrylonitrile. Condition A: DMSO was used as the sole solvent. Condition B: water was used as the sole solvent.

ity (entries 9–13). Finally, water proved to be a suitable solvent, and the use of water gave product **3aa** in an excellent yield of 97% with a diastereoselectivity of 70:30 (entry 14).

With two sets of optimized reaction conditions in hand (entries 6 and 14), we then checked the substrate scope of the reaction with regard to the Michael acceptors. As shown (Table 2), α,β-unsaturated ketones (**2a**–**2e**), esters (**2f**–**2j**), nitriles (**2k** and **2l**) and sulfones (**2m** and **2n**) all reacted with **1a** to give the desired product **3** in good to excellent yields. For the chalcones, the introduction of either an electron-donating (**2b** and **2d**) or electron-withdrawing substituent (**2c**) at the aromatic rings gave a decreased yield (**3ab**, 58–61% yield; **3ac**, 50–74% yield; **3ad**, 72–



Scheme 3. Gram-scale synthesis and the transformations of compound **3.**

74% yield), indicating that steric hindrance played an important role in determining the outcome of the reaction. The relative configuration of the major diasteromer of product **3ac** was determined through X-ray crystallography [11]. In the crystal structure, the vicinal phenyl groups adopt an *anti* orientation. Vinyl phenyl ketone **2e** also reacted as expected to give product **3ae** in a good yield (55–60% yield). For the above α,β-enones (except **2c**), the use of DMSO as the reaction solvent (condition A) gave a yield comparable to that of water (condition B). It is worth noting that only the 1,4-addition products were observed in the above addition reactions. In addition, acrylates were found to be good Michael acceptors (**2f**–**2j**), although a longer reaction time was required (2–5 h). As shown, methyl (**2f**), phenyl (**2g**), and benzyl (**2h**) acrylates as well as acrylates bearing an ether structural unit (**2i** and **2j**) were all successfully reacted and gave the corresponding products **3af**–**3aj** in 68–85% yield (Condition A). For the acrylates we examined, the use of DMSO as the reaction solvent generally gave better results than the use of water (condition B: **3af**–**3aj**, 46–71% yield). Additionally, vinyl alkyl sulfones participated in the reaction, affording products **3ak** and **3al** in very good yields (61–78% yield). Finally, acrylonitrile **2m** and crotononitrile **2n** proved to be competent substrates, giving the expected products **3am** and **3an** in moderate to very good yield (condition A: 65–80% yield; condition B: 48–83% yield).

To further investigate the generality of this reaction, acrylonitrile **2m** was used as the Michael acceptor and its addition with structural diverse 2-fluoro-2-arylacetonitriles were examined (Table 3). 2-Fluoroarylacetonitriles bearing a methoxyl (**1b** and **1c**), bromo (**1d**), chloro (**1e**), cyano (**1f**), or nitro group (**1g**) were all tolerated, leading to the target products **3am**–**3gm** in good to excellent yields. Substrates bearing an electron-withdrawing group (such as bromo, chloro and cyano) at the aromatic ring gave a higher yield (condition A: **3dm**–**3fm**, 80–94% yield) than those bearing an electron-donating group such as methoxy group (condition A: **3bm** and **3cm**, 60–65% yield). A nitro-functionalized 2-fluoronitrile **2g** also reacted and gave product **3gm** in a good yield (condition A: 67%; condition B: 58%)). For 2-fluoro-2-arylnitriles bearing a methoxy group (**2b** and **2c**), water proved to be an inappropriate solvent and a low yield was obtained (**3bm**, 35% yield; **3cm**, 45% yield). Additionally, the reaction of 2-alkylated 2-fluoroacetonitrile **1h** was also tried, but failed to give the desired product **3hm**, with the starting materials left intact. Raising the reaction temperature to 70 °C resulted in the decomposition of compound **1h**, and this may be caused by the thermal unstable nature of the corresponding fluorinated carbanion. Based on the above experiments, we have reason to believe that a synergistic stabilizing effect of the cyano and phenyl groups in fluorocarbon nucleophile **1** was important in promoting the Michael addition of 2-fluoro-2-arylacetonitriles to activated alkenes.

The current protocol can be extended to other fluorocarbon nucleophiles bearing an acyl group (Scheme 2). Under the same reaction conditions (Table 3), 2-fluoro-2-phenylacetate (**1i**), 2-fluoro-2-(4-nitrophenyl)acetate (**1j**), 2-fluoro-2-phenylacetophenone (**1k**) and cyclic 2-fluoro-1-tetralone (**1l**) were all successfully reacted to give product **3im**–**3lm** in a moderate to good yield (40–74% yield). In contrast, methyl fluoroacetate (**1m**) and 2-fluoroacetophenone (**1n**) were unreactive under the reaction conditions, further demonstrating that the stability of the corresponding fluoroenolates played a vital role in facilitating the Michael reaction.

To demonstrate the utility of our method for preparing useful organofluorine compounds, a gram-scale reaction and the diverse transformations of product **3** were conducted. Using water as the sole solvent, the Michael addition was carried out with 1.0 g 2-fluoro-2-phenylacetonitrile **1a** to give 1.18 g of the addition product **3am** (85% yield) (Scheme 3a) [12]. Treatment of the thus obtained compound **3am** with H_2O_2/K_2CO_3 led to selective oxidation of the cyano α to fluorine to deliver the corresponding amide **4** in a very good yield (86%) (Scheme 3b). The carbonyl group in the addition product also allows for useful transformations. For instance, compound **3ae** was reduced with $NaBH_4$ to give 5-hydroxyl-2-fluoronitrile **5** in an excellent yield (92%). When compound **5** was subjected to HCl/MeOH, a process involving hydrolysis of the nitrile along with intramolecular dehydration occurred and the corresponding α-fluorinated carbonyl ester **6** was obtained in 60% yield (Scheme 3c). Finally, compound **3af** could be hydrolyzed to give 4-fluoro-butanoic acid **7** in a good yield of 62%, with the cyano group left intact (Scheme 3d).

In conclusion, we have developed the first organo-catalyzed Michael addition of 2-fluoro-2-arylacetonitriles to activated alkenes, which allows an efficient synthesis of a variety of arylacetonitriles containing a fluorinated stereogenic center. This protocol uses DBU as an organocatalyst and has a broad substrate scope: α, β-unsaturated ketones, esters, nitriles and sulfones were all proved to be competent. Besides, water proved to be a good solvent for this addition reaction.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152919.

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[11] CCDC 2058429 (3ac) contain the supplementary crystallographic data for this paper.

[12] Synthetic procedure: under an air atmosphere, catalyst DBU (225 mg, 1.48 mmol) was added to a reaction mixture of acrylonitrile 2m (7.4 mmol, 0.39 g) and 2-fluoro-2-phenylacetonitrile 1a (7.4 mmol, 1.0 g) in H2O (15 mL) at 25 ℃. The reaction was reacted for 5 h, followed by extraction with ethyl acetate (10 mL × 3). The organic phase was dried over Na2SO4, filtered, and concentrated under vacuum to give the crude 3am that was purified by flash column chromatography using PE/EA (9:1) as an eluent to give the corresponding 1,4-adduct in 85% yield (1.18 g). Light yellow liquid. 1H NMR (500 MHz, CDCl3) δ 7.53 (s, 5H), 2.83–2.43 (m, 4H). 19F NMR (376 MHz, CDCl3) δ −150.71 (s). 13C NMR (126 MHz, CDCl3) δ 134.1 (d, J = 22.5 Hz), 130.7, 129.4, 124.4 (d, J = 6.3 Hz), 117.2, 115.9 (d, J = 33.9 Hz), 90.1 (d, J = 186.9 Hz), 37.2 (d, J = 25.9 Hz), 12.5 (d, J = 4.3 Hz). IR (neat) 3070, 2968, 2254, 2210, 1452, 1225, 761, 691 cm−1. HRMS (ESI): Calcd for (C11H9FN2Na) ([M+Na]+) 211.0642; found: 211.0647.