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SYNTHESIS OF TRIFLUOROMETHYL DERIVATIVES OF QUINOLINE AND ISOQUINOLINE

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Abstract – Trifluoromethyl derivatives of quinoline and isoquinoline were synthesized using phosphonium salts with a trifluoroacetamide group in the presence of 1,8-diazabicyclo[5.4.0]-7-undecene. The quinoline skeleton was formed from a phenethylphosphonium salt with a trifluoroacetamide NH proton, whereas the isoquinoline formation required masking of the amide proton of trifluoroacetamide in the benzylphosphonium structure.

Fluorinated aromatic compounds are found in various bioactive compounds, such as pharmaceuticals and pesticides. This is because the introduction of a fluorine group or a trifluoromethyl group into organic molecules causes significant changes in the chemical and pharmaceutical properties of the parent molecules.[1] Currently, the trifluoromethyl group is one of the most common fluorine-containing substituents found in commercial pharmaceuticals and agrochemicals.[2,3] Considerable efforts have been made developing synthetic strategies for introducing trifluoromethyl groups into organic skeletons. Two primary methods have been reported: (i) direct trifluoromethylating reactions using various trifluoromethylating reagents[4] and (ii) the use of pre-functionalized CF_3 group-containing building blocks.[5]

Various organofluorine compounds can be obtained by the first method using different types of trifluoromethylating reagents based on their electronic properties, such as radicality,[6] electrophilicity,[7] and nucleophilicity.[8] However, this method requires multi-step synthesis, and the trifluoromethylating reagents are sometimes difficult to handle, expensive, or both. Some studies used the second method with fluorinated building blocks, such as β-trifluoromethyl-α,β-unsaturated carbonyl compounds, which have attracted tremendous attention in recent years because of their availability and versatility.[9] By contrast, we have used trifluoroacetic acid derivatives, such as trifluoroacetic anhydride (TFAA), as a

trifluoromethyl source that is remarkably inexpensive and easy to handle, to introduce trifluoromethyl groups to a broader range of aromatic compounds. For example, our group has reported the synthesis of 2-trifluoromethylindole by the thermolysis of a phosphonium salt (Figure 1a).[10] This reaction adopts TFAA as the trifluoromethyl source, and appeared to differ from the common Wittig reaction because a strong base is not required in the reaction. This prompted further interest in the unique properties of this reaction and the application of this reaction to the construction of other heterocycles, such as quinoline and isoquinoline.[11] Interestingly, Kharrat has reported the synthesis of 2-(trifluoromethyl)quinoline with a fluorinated building block prepared from TFAA.[12] However, the systematic synthesis of various trifluoromethyl-containing heterocycles using trifluoroacetic acid derivatives has not been well developed. This paper reports the synthesis of trifluoromethyl derivatives of quinoline and isoquinoline using the same strategy as the indole formation that utilizes a trifluoroacetamide group as the trifluoromethyl source (Figure 1b). This method can contribute to expand the systematic synthesis of related heterocycles based on phosphonium-trifloroacetamide chemistry.

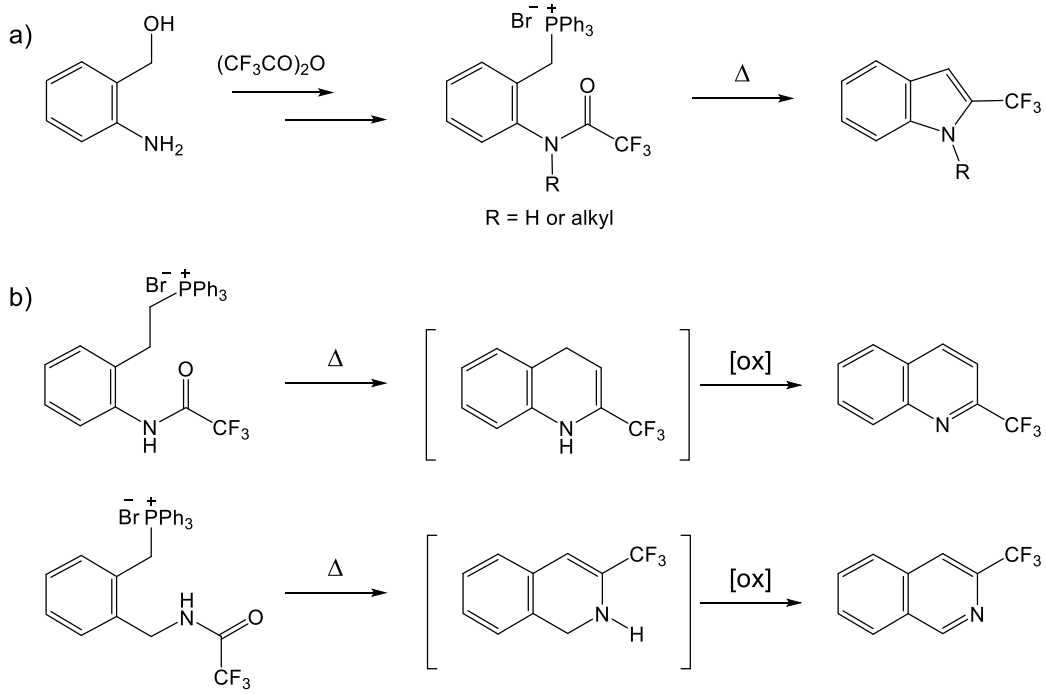
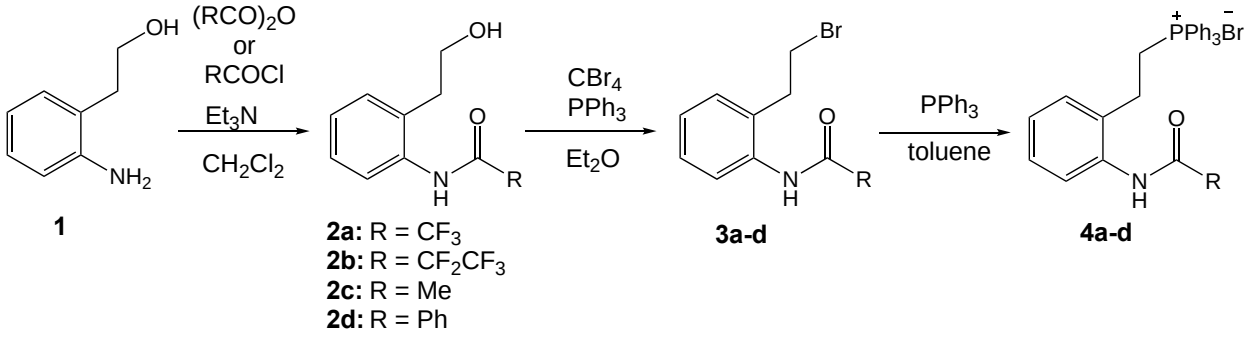


Figure 1. Synthetic strategy of trifluoromethylated heterocycles from a phosphonium salt.

SYNTHESIS OF 2-(TRIFLUOROMETHYL)QUINOLINE

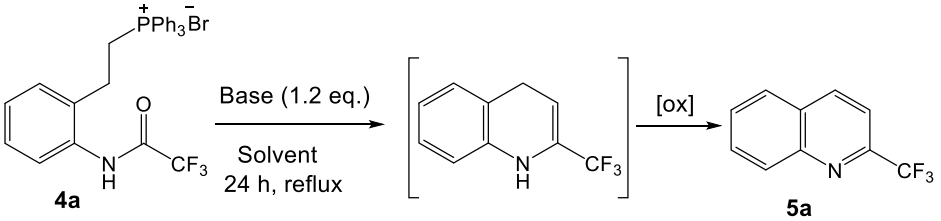
Phenethylphosphonium salts **4**, containing various *N*-acyl substituents, were synthesized, as shown in Scheme 1 (see the Experimental section and Supporting information).



Scheme 1

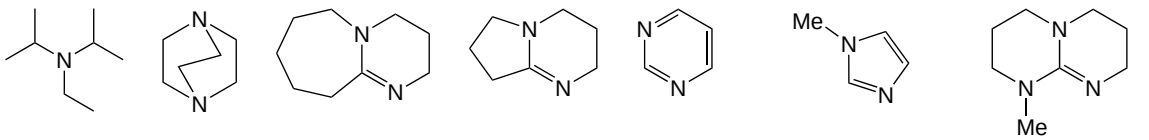
Table 1 lists the results of the cyclization reaction of a phenethylphosphonium salt **4a**. Initially, the thermolysis of **4a** under reflux in 1,2-dichlorobenzene according to indole synthesis was attempted, but quinoline **5a** was not obtained (Entry 1). Then, the addition of various amines was investigated since it was expected to be effective in a reaction mechanism we assumed (Entries 2–9). Although the reaction did not proceed under these conditions using mild basic amines, DIPEA and DABCO (Entries 2 and 3),

Table 1. Effects of bases in the synthesis of 2-(trifluoromethyl)quinoline **5a**



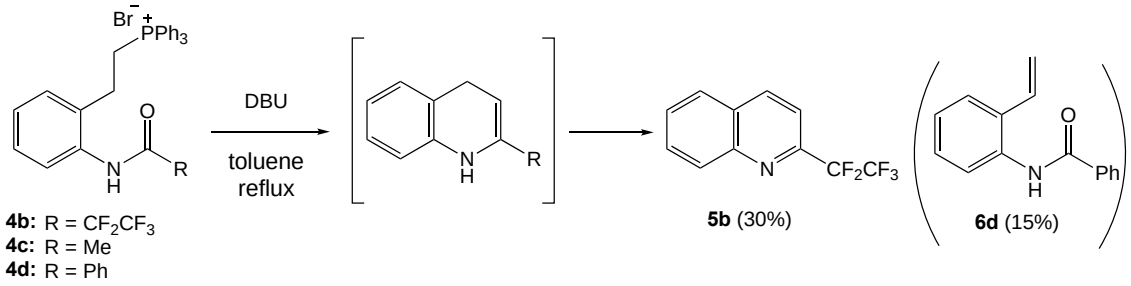
Entry	Base [a]	Solvent	Yield (%)
1	-	1,2-dichlorobenzene	no reaction
2	DIPEA	toluene	no reaction
3	DABCO	toluene	no reaction
4	DBU	toluene	50
5	DBN	toluene	50
6	MTBD	toluene	trace
7	MTBD	1,2-dichlorobenzene	19
8	pyrimidine	toluene	no reaction
9	1-methylimidazole	toluene	no reaction

[a]; Structures of bases, and their basicities (pKa values) of conjugate acids given in backets. DIPEA: *N*,*N*-diisopropylethylamine, DABCO:1,4-diazabicyclo[2.2.2]octane, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene, DBN: 1,5-diazabicyclo[4.3.0]non-5-ene, MTBD: 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene



the desired quinoline **5a** was obtained in 50% yield under these conditions using more basic amines DBU and DBN (Entries 4 and 5). Interestingly, the reaction barely proceeded when MTBD was used, which is much more basic than DBU (Entry 6); the higher reaction temperature afforded **5a** but in low yield (Entry 7). Hence, this study assessed whether the amidine skeleton might be more critical than basicity; the addition of less basic aromatic amines with an amidine structure (i.e., pyrimidine and 1-methylimidazole) was attempted (Entries 8 and 9). However, this reaction did not proceed. From the above results, it appears that an adequate but not excessively strong basic amine additive is essential for accomplishing this reaction.

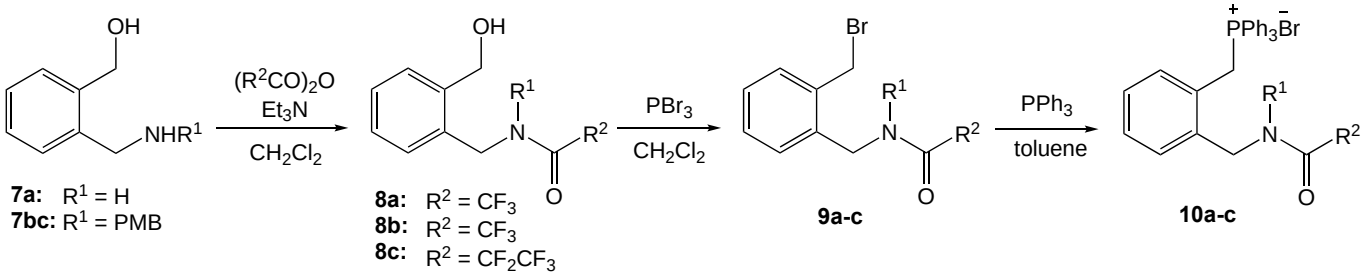
To investigate the effects of the fluorine atom, this study examined quinoline synthesis from phosphonium salts **4b-d** with different amide moieties under the DBU conditions (Scheme 2). The pentafluoroethyl derivative afforded quinoline **5b** in low yield, whereas the other derivatives did not yield the desired quinolines but afforded complex mixtures from **4c** or the β-eliminated product **6d** from **4d**. Therefore, an electron-withdrawing R group is required for this cyclization reaction.



Scheme 2

SYNTHESIS OF 3-(TRIFLUOROMETHYL)ISOQUINOLINE

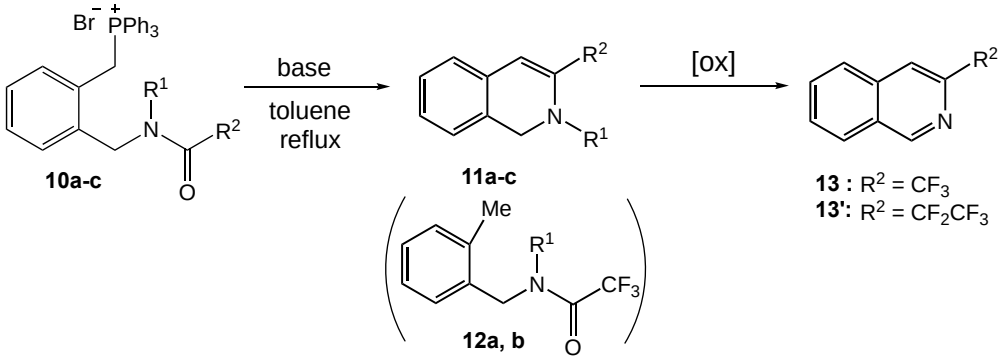
Benzylphosphonium salts **10** containing fluoroalkyl substituents were synthesized, as shown in Scheme 3 (see the Experimental section and Supporting information).



Scheme 3

Table 2 lists the results of the cyclization reaction for the benzylphosphonium salts **10a-c**. An attempt was made to synthesize isoquinoline **13** from phosphonium salt **10a** under the same conditions as the quinoline synthesis using DBU or DBN. Unexpectedly, neither the desired product **13** nor its precursor **11a** was obtained. Instead, tolyl derivative **12a** was obtained (Entries 1 and 2). It was hypothesized that the tolyl anion generated from the eight-membered ring intermediate would be protonated in situ as shown in MECHANISM section. Therefore, *N*-protected phosphonium salt **10b** was used as the substrate (Entries 3 and 4). As expected, dihydroisoquinoline **11b** was obtained in 69% yield using DBU, followed by deprotection of the PMB group with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to obtain isoquinoline **13** in 38% yield (data not shown). The yield of **13** from **10b** was improved to 87% using crude **11b** (Entry 3) because **11b** was fragile in silica gel. Interestingly, the use of DBN afforded isoquinoline **13** and the tolyl product **12b** to some extent (Entry 4). Under the DBU conditions, pentafluoroethyl derivative **13'** was obtained in 28% yield from **10c** (Entry 5).

Table 2. Effects of bases in the synthesis of 3-fluorinated isoquinoline **13**



Entry	Comp.	R^1	R^2	Base	Yield (%)
1	**10a**	H	CF_3	DBU	**12a** (69%)
2	**10a**	H	CF_3	DBN	**12a** (74%)
3	**10b**	PMB [a]	CF_3	DBU	**13** (87%)[b]
4	**10b**	PMB	CF_3	DBN	**13** (58%)[b], **12b** (40%)
5	**10c**	PMB	CF_2CF_3	DBU	**13'** (28%)[b]

[a]; *p*-methoxybenzyl group, [b]; DDQ was used as the oxidant for **11**.

MECHANISM

As, differently from 2-trifluoromethyl indole synthesis, the present trifluoromethyl substituted quinoline and isoquinoline syntheses required the organic base such as DBU, the reactions could proceed via Wittig-type ylide-formation. However, based on the results obtained, it appears to be more reasonable as described as follows. The quinoline synthesis is believed to occur via a mechanism, such as an Appel-type reaction for imidate (Figure 2). The addition of strong basic amines, such as DBU and DBN,

promoted the formation of the eight-membered ring intermediate **14** through deprotonation of the acidic trifluoroacetamide proton. The amine also assisted in eliminating phosphine oxide via an addition-elimination reaction to the imidate moiety (via **15**). Therefore, the product yield decreased when MTBD was used instead of DBU/DBN because of the lower nucleophilicity of the sterically bulky MTBD (Table 1, Entries 6 vs. 4 and 5). The resulting compound **16** was oxidized spontaneously in air to afford quinoline **5a**. The trifluoromethyl group preferably improves the acidity of the amide proton of **4** and the electrophilicity of the neighboring sp^2 carbon of **14** due to the electron-withdrawing effect of fluorine atoms. It would be the reason why methyl and phenyl derivatives (**4c** and **4d**) did not afford the quinoline structures.

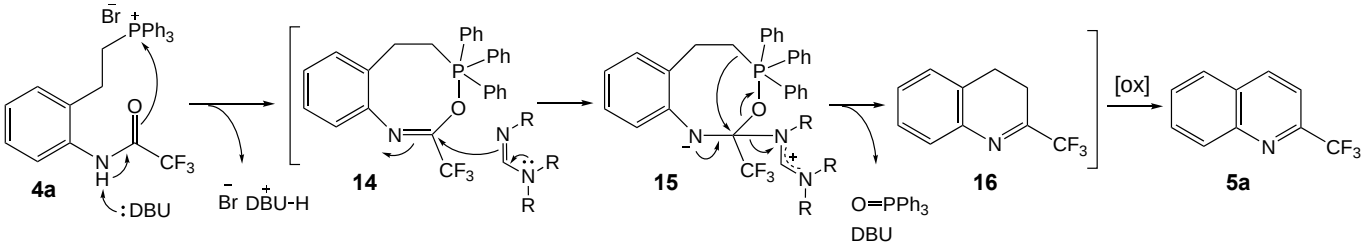


Figure 2. Possible reaction mechanism from **4a** to **5a**

The unexpected tolyl product **12a** in isoquinoline synthesis was formed via a similar mechanism to that from quinoline synthesis (Figure 3a). In the case of the isoquinoline synthesis, the benzyl anion generated by eliminating phosphine oxide was likely protonated instead of the substitution with the amidinium moiety, probably because of the stable nature and low nucleophilicity of the benzyl anion. The protonated intermediate **15** was finally hydrolyzed to produce **12a**. This undesirable pathway was controlled by masking the amide proton like PMB derivative **10b** to form the dihydroisoquinoline skeleton. Dihydroisoquinoline **11b** was probably formed by a Wittig-type cyclization reaction via ylide **16** (Figure 3b, path A) because **10b** does not have an acidic trifluoroacetamide proton. However, the former pathway seems to exist even with the *N*-protected substrate (Table 2, Entry 4), which might proceed via an iminium intermediate **17**, such as path B.

In conclusion, the trifluoromethyl derivatives of quinoline and isoquinoline were synthesized using phosphonium salts with trifluoroacetamide groups as the trifluoromethyl sources. The quinoline skeleton was synthesized, possibly via an eight-membered cyclic phosphonium alkoxide intermediate with the addition of strong basic amines, such as DBU. However, the formation of isoquinoline required masking of the amide proton of the trifluoroacetamide, and it was believed to be formed by a Wittig-type

cyclization reaction. The development of these reactions will help expand the systematic synthesis of related heterocycles based on phosphonium-trifloroacetamide chemistry.

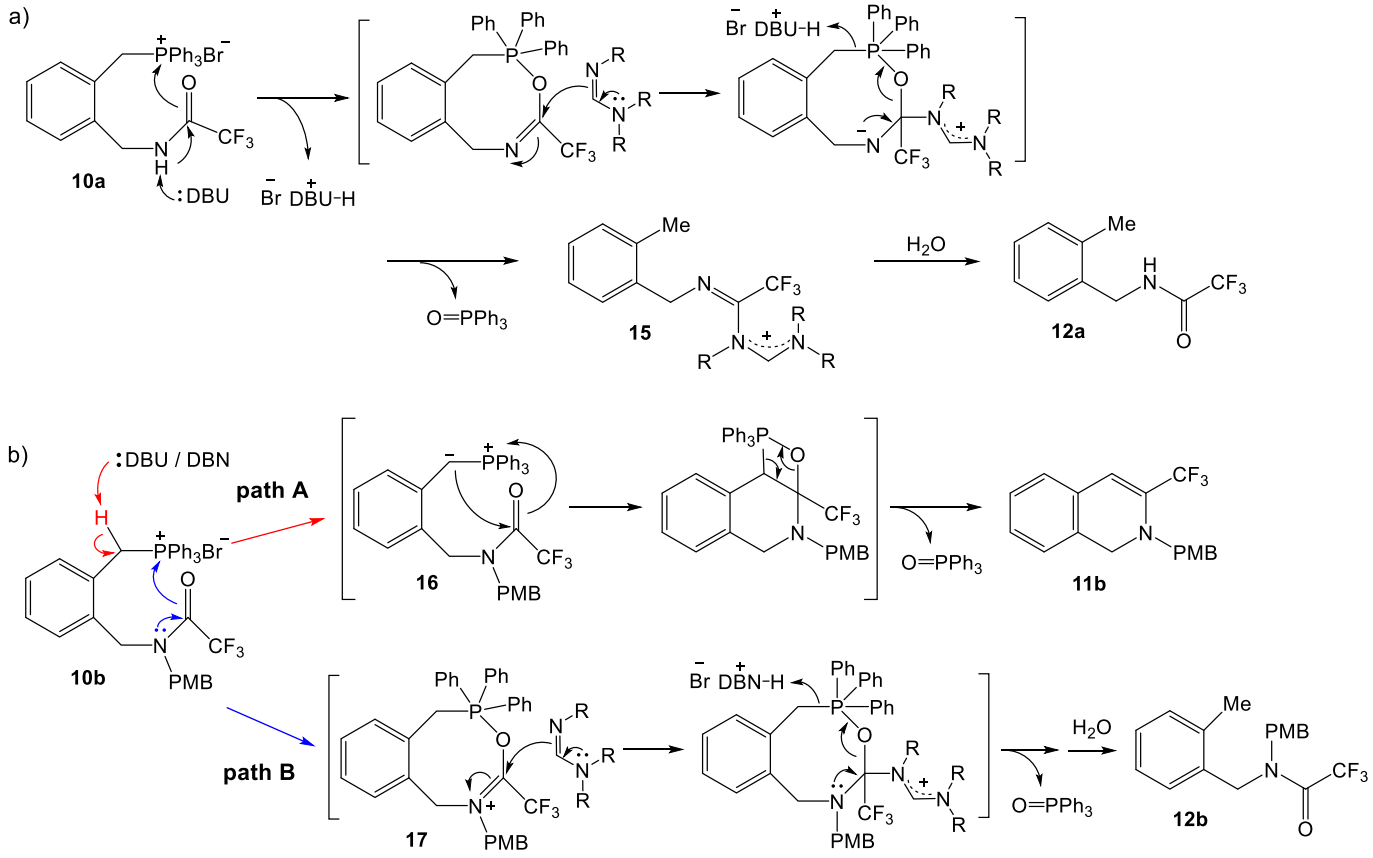


Figure 3. Two possible reaction pathways from **10**

EXPERIMENTAL

General information

^{1}H- and ^{13}C- NMR spectra were recorded on a JNM-ECZ400S spectrometer at 400 and 100 MHz, respectively, and chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane or the solvent signal. ^{19}F NMR spectra were recorded on a JNM-ECZ400S spectrometer at 380 MHz with hexafluorobenzene (0 ppm) as an internal standard. Mass spectra were recorded using a JEOL JMS-T100LP mass spectrometer in the positive electrospray ionization (ESI) mode. Melting point (Mp) values were measured using a Yanaco melting point apparatus. Notably, the obtained Mp values were not corrected. Column chromatography was performed using a Fuji Silysia PSQ 100 silica gel or Teledyne Isco RediSep Rf silica gel.

General procedure for the synthesis of 2-substituted phenethyltriphenylphosphonium bromides 4a-d

A solution of the bromide **3a-d** (2.0 mmol) and PPh_3 (1.5 g, 6.0 mmol) in toluene (5 mL) was stirred under reflux overnight. After cooling, the precipitate was collected by filtration, washed with dry Et_2O, and dried under reduced pressure to afford phosphonium salt **4a-d**.

Triphenyl(2-(2,2,2-trifluoroacetamido)phenethyl)phosphonium bromide (4a)

89% yield, white solid, Mp 242 -244 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.79-2.85 (2H, m), 4.09-4.17 (2H, m), 7.07 (1H, d, *J* = 8.4 Hz), 7.20 (1H, dt, *J* = 7.3 Hz, 1.9 Hz), 7.25-7.31 (2H, m), 7.69-7.74 (6H, m), 7.80-7.92 (9H, m), 11.34 (1H, brs). ^{13}C-NMR ($CDCl_3$) δ: 24.5, 24.5, 24.8, 25.3, 116.0 (q, *J* = 287.5 Hz), 117.2, 118.0, 128.4, 128.6, 129.4, 129.7, 130.4, 130.7, 133.2, 133.5, 133.6, 135.1, 135.2, 135.4, 135.6, 157.4 (q, *J* = 37.4 Hz). HRMS (ESI) calcd for Chemical Formula: $C_{28}H_{24}BrF_3NOP$ $[M\text{-}Br]^-$ 478.1542; found 478.1524.

(2-(2,2,3,3,3-Pentafluoropropanamido)phenethyl)triphenylphosphonium bromide (4b)

97% yield, white solid, Mp 271-273 °C. ^{1}H-NMR (CD_3OD) δ: 2.90-2.96 (2H, m), 2.73-3.80 (2H, m), 7.21 (1H, dd, *J* = 7.6 Hz, 1.6Hz), 7.34-7.42 (2H, m), 7.53 (1H, dd, *J* = 7.2 Hz, 2.0 Hz), 7.75-7.85 (12H, m), 7.89-7.94 (3H, m). ^{13}C-NMR (CD_3OD) δ: 23.0, 23.5 24.6, 24.6, 108.3 (tq, *J* = 264.5 Hz, 38.3 Hz), 118.8, 119.3 (qt, *J* = 284.6 Hz, 34.5 Hz), 119.7, 128.6, 129.2, 130.0, 130.8, 131.6, 131.7, 133.8, 134.8, 134.9, 136.4, 136.4, 136.5, 136.5, 158.7, 158.7 (t, *J* = 25.9 Hz). HRMS (ESI) calcd for $C_{29}H_{24}BrF_5NOP$ $[M\text{-}Br]^-$ 528.1510; found 528.1506.

(2-Acetamidophenethyl)triphenylphosphonium bromide (4c)

98% yield, pale yellow solid, Mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.21 (3H, s), 2.89-2.96 (2H, m), 3.84-3.91 (2H, m), 6.99 (1H, d, *J* = 8.0 Hz), 7.06 (1H, t, *J* = 7.2 Hz), 7.17 (1H, dt, *J* = 7.2 Hz, 1.2 Hz), 7.30 (1H, d, *J* = 7.2 Hz), 7.65-7.74 (6H, m), 7.81-7.88 (9H, m), 10.15 (1H, brs). ^{13}C-NMR ($CDCl_3$) δ: 23.5, 24.97, 25.1, 25.2, 117.3, 118.1, 127.0, 128.1, 129.2, 129.3, 130.4, 130.5, 133.6, 133.7, 134.8, 135.0, 135.1, 135.1, 136.1, 171.1. HRMS (ESI) calcd for $C_{28}H_{27}BrNOP$ $[M\text{-}Br]^-$ 424.1825; found 424.1817.

(2-Benzamidophenethyl)triphenylphosphonium bromide (4d)

92% yield, pale yellow solid, Mp >300 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.80-2.86 (2H, m), 3.96-4.03 (2H, m), 7.11-7.15 (2H, m), 7.20 (1H, dt, *J* = 8.0 Hz, 2.8 Hz), 7.27 (1H, d, *J* = 8.0 Hz), 7.43-7.50 (8H, m), 7.53-7.57 (1H, m), 7.63-7.66 (3H, m), 7.73-7.79 (6H, m), 8.43 (2H, d, *J* = 6.8 Hz), 10.55 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 24.6, 25.0, 25.2, 117.3, 118.1, 127.7, 128.2, 128.3, 128.8, 129.4, 130.0, 130.2, 130.3, 131.5, 133.1, 133.3, 133.5, 134.8, 134.8, 136.3, 136.4, 170.0. HRMS (ESI) calcd for $C_{33}H_{29}BrNOP$ $[M\text{-}Br]^-$ 486.1981; found 486.1969.

2-(Trifluoromethyl)quinoline (5a)

A mixture of **4a** (300 mg, 0.57 mmol) and DBU (0.16 mL, 1.14 mmol) in toluene (6 mL) was stirred under reflux for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane = 1/40) to give **5a** (53 mg, 50%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 7.67 (1H, td, *J* = 8.0 Hz, 1.2 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 7.87 (1H, td, *J* = 8.0 Hz, 1.2 Hz), 7.90 (1H, d, *J* = 8.0 Hz), 8.23 (1H, d, *J* = 8.8 Hz), 8.35 (1H, d, *J* = 8.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 116.7, 121.5 (q, *J* = 274.0 Hz), 127.7, 128.6, 128.8, 130.0, 130.8, 138.1, 147.1, 147.8 (q, *J* = 34.5 Hz). ^{19}F-NMR ($CDCl_3$) δ: 94.2. HRMS (ESI) calcd for $C_{10}H_7F_3N$ $[M+H]^+$ 198.0525; found 198.0533.

2-(Perfluoroethyl)quinoline (5b)

A mixture of **4b** (300 mg, 0.49 mmol) and DBU (0.22 mL, 1.50 mmol) in toluene (3 mL) was stirred under reflux for 24 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc /hexane = 1/100) to give **5b** (37 mg, 30%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 7.69 (1H, td, *J* = 8.0 Hz, 1.2 Hz), 7.76 (1H, d, *J* = 8.0 Hz), 7.84 (1H, td, *J* = 8.0 Hz, 1.2 Hz), 7.92 (1H, d, *J* = 8.0 Hz), 8.25 (1H, d, *J* = 8.8 Hz), 8.37 (1H, d, *J* = 8.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 111.3 (tq, *J* = 254.0 Hz, 37.4 Hz), 117.9, 120.4 (qt, *J* = 285.6 Hz, 37.4 Hz), 127.6, 128.7, 130.3, 130.3, 130.8, 137.9, 147.3, 147.4 (t, *J* = 25.4 Hz). ^{19}F-NMR ($CDCl_3$) δ: 44.9, 78.9. HRMS (ESI) calcd for $C_{11}H_7F_5N$ $[M+H]^+$ 248.0493; found 248.0490.

General procedure for the synthesis of (2-substituted benzyl)triphenylphosphonium bromides 10a-c

A solution of bromide **9a-c** (1.0 mmol) and PPh_3, (0.30 g, 1.2 mmol) in toluene (5 mL) was stirred under reflux for 6 h. After cooling, the precipitate was collected by filtration, washed with dry Et_2O, and dried under reduced pressure to afford phosphonium salt **10a-c**.

Triphenyl(2-((2,2,2-trifluoroacetamido)methyl)benzyl)phosphonium bromide (10a)

96% yield, white solid, Mp >300 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.63 (2H, d, *J* = 4.8 Hz), 5.25 (2H, d, *J* = 15.2 Hz), 7.01 (1H, d, *J* = 7.2 Hz), 7.16 (1H, t, *J* = 7.2 Hz), 7.23 (1H, d, *J* = 7.6 Hz), 7.34 (1H, t, *J* = 7.2 Hz), 7.64 (3H, d, *J* = 7.6 Hz), 7.67 (3H, d, *J* = 7.6 Hz), 7.74 (3H, t, *J* = 7.6 Hz), 7.75 (3H, t, *J* = 7.6 Hz), 7.92 (3H, t, *J* = 7.6 Hz), 9.94 (1H, s). ^{13}C-NMR (DMSO-d_6) δ: 25.5, 26.0, 115.8 (q, *J* = 286.5 Hz), 116.9, 117.7, 125.9, 126.0, 128.1, 128.1, 129.0, 129.1, 129.8, 129.8, 130.2, 130.3, 131.2, 131.3, 133.9, 134.0, 135.3, 135.3, 137.7, 137.8, 156.2 (q, *J* = 36.5 Hz). HRMS (ESI) calcd for $C_{28}H_{24}F_3NOP$ $[M-Br]^-$ 478.1548; found 478.1538.

Triphenyl(2-((2,2,2-trifluoro-*N*-(4-methoxybenzyl)acetamido)methyl)benzyl)phosphonium bromide (10b)

96% yield, diastereomeric mixtures 1/3, white solid, Mp 238-240 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.42 (0.5H, s),

3.60 (1.5H, s), 3.86 (2.25H, s), 3.91 (0.75H, s), 4.35 (2H, s), 5.12 (0.5H, d, *J* = 14.2 Hz), 5.18 (1.5H, d, *J* = 14.2 Hz), 6.99-7.27 (7H, m), 7.46-7.65 (13H, m), 7.77-7.81 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 26.8, 27.0, 27.3, 27.5, 43.6, 44.3, 47.8, 48.4, 55.3, 55.5, 114.6, 114.8, 116.3 (q, *J* = 286.5 Hz), 116.4, 116.5, 117.2, 117.3, 125.0, 125.6, 125.7, 126.0, 126.4, 126.5, 127.8, 128.7, 129.0, 129.1, 129.2, 129.2, 130.0, 130.1, 130.2, 130.2, 130.5, 130.5, 132.7, 132.8, 133.8, 133.9, 134.0, 134.0, 134.3, 134.3, 134.7, 134.7, 135.1, 135.1, 157.2 (q, *J* = 35.4 Hz), 159.3, 159.4. HRMS (ESI) calcd for $C_{36}H_{32}F_3NOP$ $[M-Br]^-$ 598.2117; found 598.2116.

(2-((2,2,3,3,3-Pentafluoro-*N*-(4-methoxybenzyl)propanamido)methyl)benzyl)triphenylphosphonium bromide (10c)

88% yield, diastereomeric mixtures 1/3, pale yellow amorphous, ^{1}H-NMR ($CDCl_3$) δ: 3.53 (0.5H, s), 3.61 (1.5H, s), 3.85 (2.25H, s), 3.89 (0.75H, s), 4.35 (0.5H, s), 4.38 (1.5H, s), 5.01 (1.5H, d, *J* = 14.4 Hz), 5.07 (0.5H, d, *J* = 14.4 Hz), 6.91 (1H, d, *J* = 7.6 Hz), 6.99-7.11 (4H, m), 7.20 (1H, t, *J* = 7.6 Hz), 7.28 (1H, t, *J* = 7.6 Hz), 7.46 (1H, d, *J* = 7.6 Hz), 7.50-7.56 (6H, m), 7.61-7.65 (6H, m), 7.79-7.83 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 26.8, 27.0, 27.3, 27.4, 43.3, 44.2, 47.7, 48.1, 55.4, 55.6, 108.4 (tq, *J* = 270.8 Hz, 36.4 Hz), 114.7, 114.9, 116.3, 116.6, 117.2, 117.4, 118.2 (qt, *J* = 282.7 Hz, 33.5 Hz), 125.1, 125.6, 125.7, 126.0, 126.5, 126.6, 127.7, 128.7, 129.2, 129.2, 129.3, 129.4, 129.4, 129.4, 130.1, 130.1, 130.2, 130.3, 130.9, 130.9, 132.8, 132.9, 133.8, 133.9, 134.0, 134.1, 134.3, 134.4, 134.6, 134.6, 135.2, 135.2, 158.1 (t, *J* = 24.9 Hz), 159.4, 159.5. HRMS (ESI) calcd for $C_{37}H_{32}F_5NOP$ $[M-Br]^-$ 648.2085; found 648.2091.

2,2,2-Trifluoro-N-(2-methylbenzyl)acetamide (12a)

A mixture of **10a** (50 mg, 0.092 mmol) and DBU (22.0 μL, 0.2 mmol) in toluene (1 mL) was stirred under reflux for 3 h. After cooling to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane = 1/3) to give **12a** (13 mg, 69%) as a white amorphous. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 4.50 (2H, d, *J* = 5.2 Hz), 6.59 (1H, brs), 7.16-7.27 (4H, m). ^{13}C-NMR ($CDCl_3$) δ: 18.9, 42.0, 116.0 (q, *J* = 28.6 Hz), 126.5, 128.6, 128.8, 130.8, 133.5, 136.5, 157.1 (q, *J* = 37.3 Hz). HRMS (ESI) calcd for $C_{10}H_{10}F_3NNaO$ $[M+Na]^+$ 240.0607; found 240.0893.

3-(Trifluoromethyl)isoquinoline (13)

A mixture of **10b** (280 mg, 0.42 mmol) and DBU (75 μL, 0.50 mmol) in toluene (2 mL) was stirred under reflux for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure. DDQ (280 mg, 1.3 mmol) was added to a stirred residue solution in CH_2Cl_2 (3 mL) at room temperature. The resulting mixture was stirred for 48 h at room temperature, quenched with saturated aqueous $NaHCO_3$ solution, and separated the layers. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (EtOAc /hexane =

1/100) to give **13** (71 mg, 87%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 7.75 (1H, td, *J* = 7.5, 1.3 Hz), 7.81 (1H, td, *J* = 7.5, 1.3 Hz), 7.93 (1H, d, *J* = 8.4 Hz), 8.05 (1H, d, *J* = 8.0 Hz), 8.07 (1H, s), 9.30 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 118.3(q, *J* = 3.3 Hz), 122.2 (q, *J* = 266.7 Hz), 127.5, 127.7, 129.4, 129.4, 131.6, 135.1, 141.6 (q, *J* = 34.5 Hz), 153.1. ^{19}F-NMR ($CDCl_3$) δ: 94.4. HRMS (ESI) calcd for $C_{10}H_7F_3N$ $[M+H]^+$ 198.0525; found 198.0522.

3-(Perfluoroethyl)isoquinoline (13')

A mixture of **10c** (170 mg, 0.23 mmol) and DBU (41 μL, 0.27 mmol) in toluene (1 mL) was stirred under reflux for 1 h. After cooling to room temperature, the solvent was removed under reduced pressure. DDQ (160 mg, 0.69 mmol) was added to a stirred residue solution in CH_2Cl_2 (2 mL) at room temperature. The mixture was stirred for 72 h at room temperature, quenched with saturated aqueous $NaHCO_3$ solution, and separated the layers. The aqueous layer was extracted twice with CH_2Cl_2, and the combined organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (EtOAc/hexane = 1/100) to give **13'** (16 mg, 28%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 7.79 (1H, td, *J* = 7.5, 1.5 Hz), 7.84 (1H, td, *J* = 7.5, 1.5 Hz), 7.98 (1H, d, *J* = 8.4 Hz), 8.09 (1H, d, *J* = 8.4 Hz), 8.14 (1H, s), 9.36 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 111.7 (tq, *J* = 253.0, 37.4 Hz), 119.1 (qt, *J* = 284.7, 38.3 Hz), 120.3 (t, *J* = 5.3 Hz), 127.5, 127.8, 129.4, 129.6, 131.6, 135.2, 141.1 (t, *J* = 24.9 Hz), 153.0. ^{19}F-NMR ($CDCl_3$) δ: 45.0, 78.7. HRMS (ESI) calcd for $C_{11}H_7F_5N$ $[M+H]^+$ 248.0493; found 248.0491.

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