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Synthesis of 4-Trifluoromethylpyridines by [5+1] Cyclization of 3-Hydroxy-pent-4-yn-1-ones with Urea

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Abstract: Trifluoromethyl-substituted 1,3-diketones can undergo direct alkynylation reactions which are not possible for alkyl- or aryl-substituted derivatives. The products can be easily transformed into 2,6-diaryl-4-trifluoromethylpyridines by acid-mediated [5+1] cyclization with urea. The reaction was thoroughly optimized by variation of the conditions and the scope was studied in detail. The products are not readily available by other methods. A plausible mechanism was suggested based on DFT calculations.

Keywords: alkynes; cyclization; fluorine; pyridines; urea

Despite the numerous approaches to the synthesis of pyridines that have been developed throughout decades, alternative pathways continue to emerge because pyridines are very important lead structures in medicinal chemistry and material science. Classical methods for the synthesis of pyridines include the formal [5+1] cyclocondensation of 1,5-dicarbonyl species or their analogues with ammonia or related compounds,[1] the Diels–Alder reaction of dienophiles with azines,[2] and the condensation of enamine derivatives with dielectrophiles.[3] Much attention is being paid nowadays to the synthesis of pyridines by transition metal-catalyzed reactions. This includes gold-catalyzed reactions of propargyl vinyl ethers,[4] β-keto esters and propargylic amines,[5] [4+2] or [2+2+2] cycloadditions of alkynes, dienes or nitriles,[6] and Suzuki or Sonogashira reactions.[7] Despite recent advances in the field, the introduction of the (pharmacologically very important) trifluoromethyl group to pyridines remains a challenging goal. A number of trifluoromethylated pyridines have been reported to show remarkable pharmacological properties. For example, pyridine-derived scaffolds **1a** and **1b** are considered as efficient mGluR2 antagonists;[8] bis-(indolyl)-4-trifluoromethylpyridines **2** are promising anti-cancer agents (Figure 1).[9]

Moreover, trifluoromethylated pyridines have been applied in the field of agrochemistry. For example, picoxystrobin™, containing a 2-trifluoromethylpyridine fragment, is a widely used fungicide, which is produced by DuPont.

In many cases, a Pd- or Cu-catalyzed trifluoromethylation of a heterocyclic moiety using $TMSCF_3$ can be carried out,[10] however, these methods require

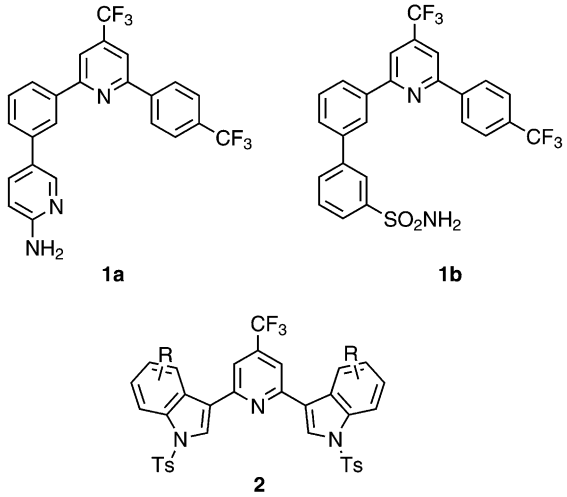
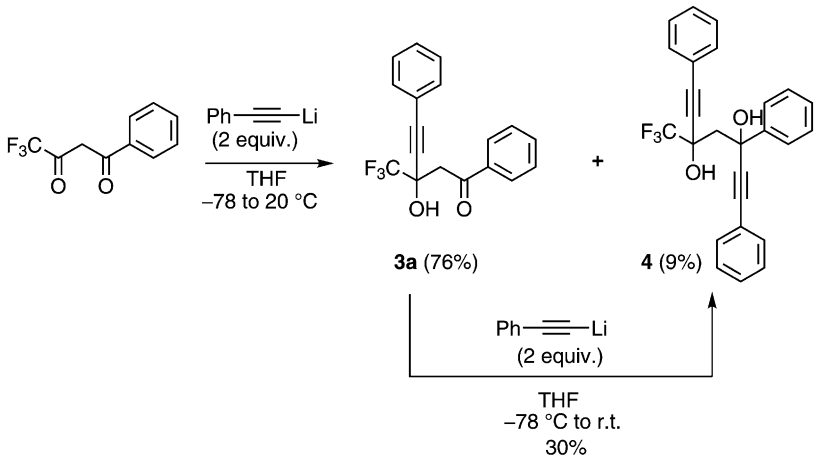


Figure 1. Pharmacologically relevant 4-trifluoromethylpyridines.



Scheme 1. Reaction of lithiated phenylacetylene with 3-benzoyl-1,1,1-trifluoroacetone.

comparatively complicated catalytic systems and are rather expensive. In recent times, a number of elegant methods for the trifluoromethylation of pyridines have been developed. This includes oxidative C–H trifluoromethylation,[11] implementation of photoredox catalysis,[12] and rhenium-catalyzed trifluoromethylation by hypervalent iodine derivatives[13]. Another remarkable possibility is based on the multistep synthesis of 4-trifluoromethylpyridines, developed by Jiang and co-workers, starting from ethyl trifluoroacetate and allyl bromide. However, this protocol suffers from low overall yields.[14] Herein, we report an unprecedented two-step procedure which relies on the reaction of trifluoromethyl-substituted 1,3-diketones with lithiated alkynes and subsequent formal [5+1]cyclocondensation with urea.

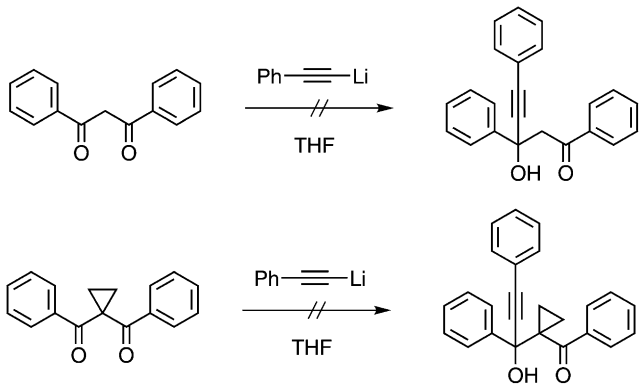
It occurred to us that 3-hydroxypent-4-yn-1-ones, containing a carbonyl group and a propargylic alcohol fragment, might be attractive 1,5-dielectrophilic synthons which could form pyridines upon reaction with a nitrogen source. This type of formal [5+1]cyclocondensation has, to the best of our knowledge, not been previously studied.

Thus, our first task was to develop a straightforward route to the corresponding starting materials. Obviously, the direct alkynylation of 1,3-diketones, which leads to monoaddition products, would be the easiest method. However, to the best of our knowledge, only very few examples of such transformations have been previously reported in the literature and all of them include reactions of 2,2-disubstituted 1,3-diketones, such as dialkylated ninhydrins, and products are bisadducts.[15] For 1,3-diketones containing an unsubstituted CH_2 group, one-step double additions are impossible, due to the highly prevailing enol form (in most organic solvents). The electrophilic nature of the enol is very low and the electrophilicity of the remaining carbonyl group is also highly reduced because of the conjugated enol fragment. In addition, the reaction of lithiated alkynes with 1,3-diketones can result in a competing deprotonation of the CH-acidic methylene group. We supposed, that the presence of a highly electron-withdrawing substituent, such as a trifluoromethyl group, and the use of an excess of the lithiated alkyne could result in the formation of the desired monoalkynylated product. With this concept in mind, we started our investigations.

To our delight, the reaction of 2 equiv. of lithiated phenylacetylene, generated by LDA, with 3-benzoyl-1,1,1-trifluoroacetone, proceeded smoothly and afforded 3-hydroxy-1,5-diphenyl-3-(trifluoromethyl)-pent-4-yn-1-one (**3a**) in 76% yield (Scheme 1). The formation of the product can be explained by deprotonation of the substrate by the first equivalent of the acetylide and subsequent attack of the second equivalent of the acetylide to the carbonyl group. The bisadduct **2** was isolated as a side-product in 9% yield. The reaction of the monoadduct with 2 equiv. of lithiated phenylacetylene resulted in the formation of bisadduct **4** in 30% yield (Scheme 1). We tried to use different bases (NaH, LDA) to replace the lithiated alkyne in the first deprotonation step, in order to avoid the use of 2 equiv of the alkyne. These experiments proved to be unsuccessful (formation of a complex mixture). All attempts to use non-fluorinated 1,3-diketones, such as dibenzoylmethane (Scheme 2) under identical conditions, failed which supports our initial concept. Moreover, initial alkynylation of cyclopropanated dibenzoylmenthane (which was prepared to avoid enolization of the corresponding diketone) did not result in formation of the desired product, most probably due to decomposition of the starting material through a retro-Claisen reaction.

Inspired by our first successful experiment, we studied the alkynylation of a number of 1,3-diketones using different acetylene derivatives (Figure 2).

Most of the products **3a–t** were isolated in good yields. The synthesis of products **3s** and **3t**, derived



Scheme 2. Unsuccessful alkynylation of dibenzoylmethanes.

from 1,1,1-trifluoroacetylacetone, required the use of 10 mol% of $Zn(OTf)_2$. All products **3** were stable, except from derivatives **3s** and **3t** which easily decomposed and, thus, had to be used without purification.

With these results in hand, we studied next the transformation of 3-hydroxy-1,5-diaryl-3-(trifluoromethyl)pent-4-yn-1-ones into pyridines. The first and main problem was to identify a suitable nitrogen source. In comparison to 1,5-dicarbonyl compounds, which are used in cyclocondensations with ammonia,[1] 3-hydroxy-pent-4-yn-1-ones are reactive only in acidic media, because a propargyl cation must be formed. Therefore, the use of ammonia is not suitable, because of its lack of acidity. On the other hand, the employment of ammonium acetate is also not pos-

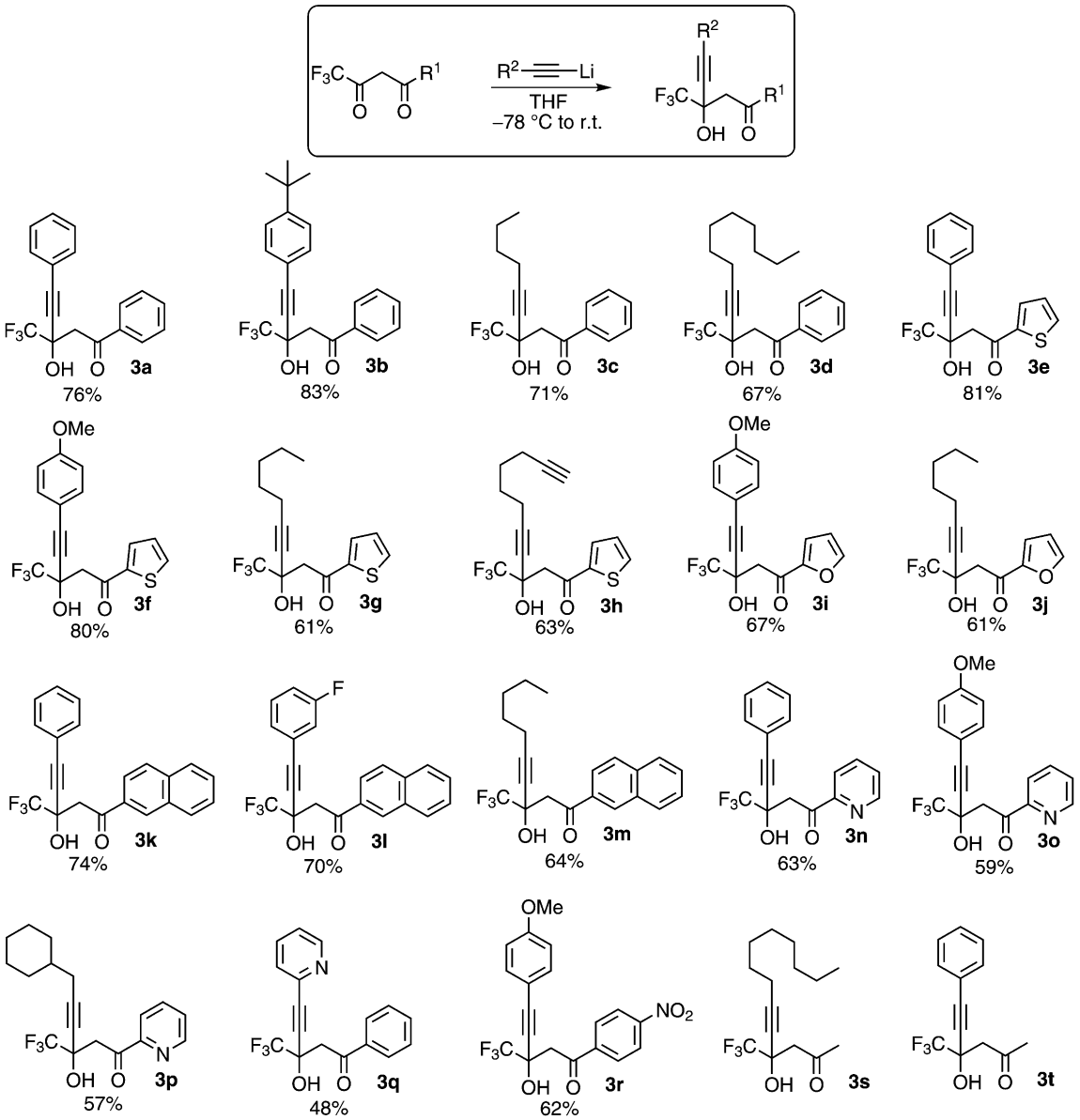


Figure 2. Structures of **3a–t**.

Table 1. Optimization of the reaction conditions.

Entry	Acid	Solvent	Time [h][a]	Yield of **5a** [%]
1	PTSA (2.0 equiv.)	toluene	20	6
2	TfOH (2.0 equiv.)	toluene	7	39
3	TFA (2.0 equiv.)	toluene	12	47
4	MsOH (2.0 equiv.)	toluene	7	34
5	AcOH (2.0 equiv.)	toluene	24	18
6	TFA (3.5 equiv.)	toluene	12	68
7	TFA (3.5 equiv.)[b]	toluene	12	68
8	TFA (3.5 equiv.)	DCE	15	41
9	TFA (3.5 equiv.)	$MeNO_2$	5	9

[a] The reaction was stopped after complete conversion of the starting material.
[b] 4 Å MS was used.

sible, because of its low nucleophilicity. As an alternative, we turned our attention to urea, which has a number of advantages in comparison to ammonia. On the one hand, urea is much less basic than ammonia. On the other hand, it is quite nucleophilic in its electroneutral form and also keeps some nucleophilicity in the presence of acid (as it is protonated at the oxygen atom). At the same time, its amide residue can be cleaved during the cyclization process under acidic conditions.

As a starting point, we have tested the use of toluene and *p*-toluenesulfonic acid (PTSA) as solvent and catalyst, respectively. The acid was used in excess (2 equiv.). Besides its catalytic role, it also serves as a proton donor in the cyclization process, because it protonates the nitrogen source. However, reflux (up to 20 h) of a mixture of **3a**, urea (1.2 equiv.) and PTSA (2 equiv.) resulted in a poor yield of the desired pyridine (Table 1). Screening of a number of Brønsted acids revealed that trifluoroacetic acid was most efficient. Increasing the amount of acid (3.5 equiv.) also resulted in better yields (entry 6). Employment of other solvents, such as DCE or nitromethane, resulted in a drastic decrease of the yield.

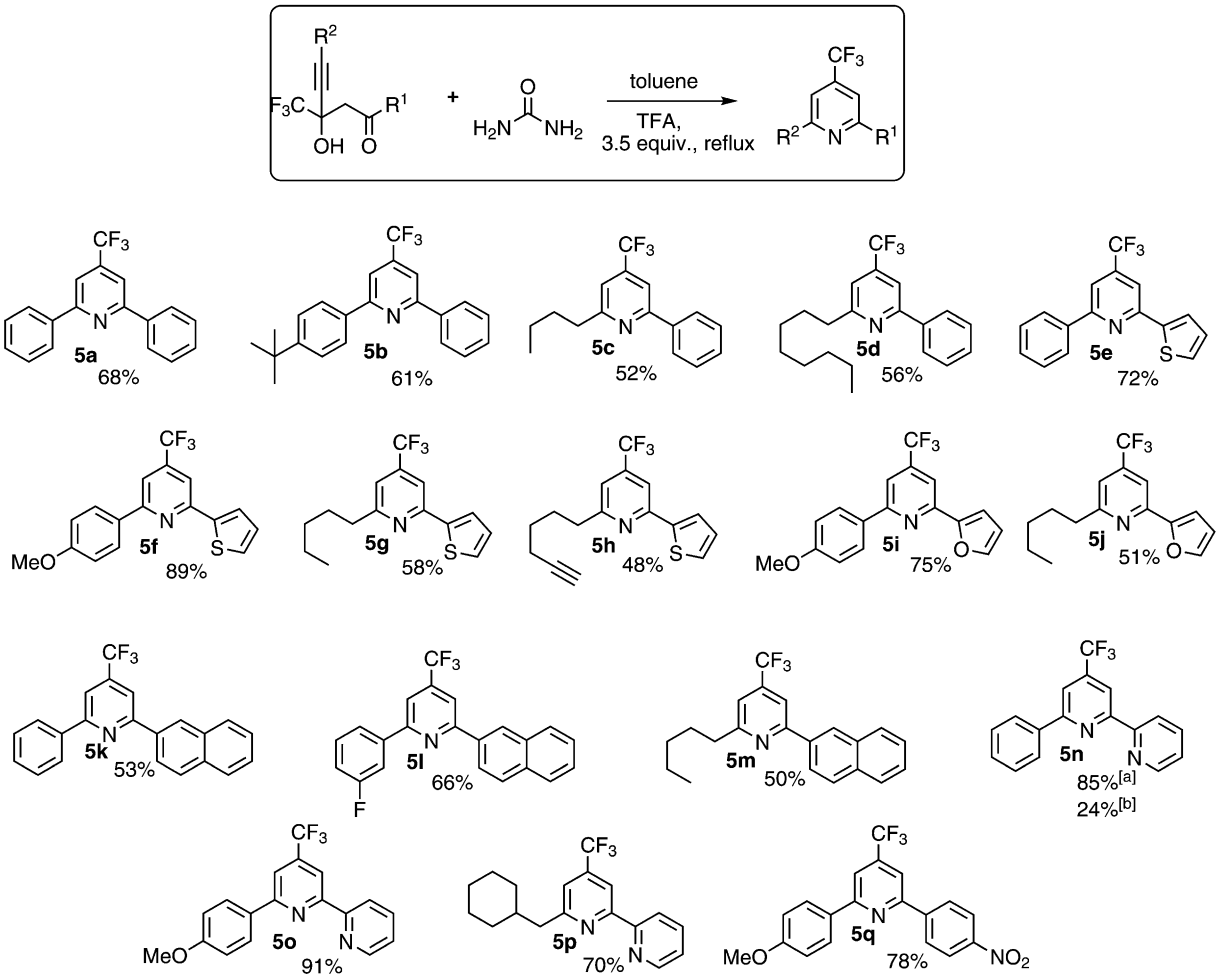
It is important to mention that our attempts to prepare the target molecules by a one-pot procedure were unsuccessful (formation of complex mixtures). This might be explained by the fact that the acetylene, which is used in excess, can react with the propargylic alcohol under acidic conditions to give 1,4-diynes. This type of process has been previously reported.[16]

The preparative scope of the cyclization was next studied. The electronic properties of the substituents attached to the keto group and to the triple bond show a remarkable influence on the reaction time and yield (Figure 3). The best results were obtained when electron-rich alkynes were used and when the π-donating properties of the substituent located at the keto group are comparatively weak. Obviously, this might be explained by carbocation stabilization in the case of a π-donating group located at the triple bond and the higher reactivity of the carbonyl group attached to an electron-withdrawing substituent. This is illustrated by the observation that pyridine **5n** is obtained in 85% yield after 2 h, starting from **3n**, while, starting from **3q**, the same product was formed in only 24% yield and required prolonged heating up to 14 h. Starting with **3s** and **3t**, unfortunately, no product could be isolated under various conditions.

To extend the scope of our method, we attempted to synthesize 2-aryl-4-trifluoromethylpyridines as well as 4-carboxymethylpyridines, starting from appropriate building blocks (Scheme 4). The use of 4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**6**) proved to be unsuccessful, presumably because of the decreased electrophilicity of the carbonyl group (due to the electronic influence of the ethoxy group). Therefore, we prepared the corresponding acetal **7**,[17] which should allow for the synthesis of 6-unsubstituted 4-trifluoromethylpyridines. Despite the fact, that alkynylation of **7** proceeded smoothly, the following cyclization was unsuccessful under various conditions. Unfortunately, alkynylation of benzoylpyruvate **9** also failed.

The structure of product **5q** was independently confirmed by X-ray crystal structure analysis (Figure 4). The pyridine ring and the phenyl groups are in one plane.

To gain mechanistic insight for the acid-catalyzed formation of pyridine **5a** (Scheme 3), DFT calculations have been performed (for details, see the Supporting Information). The starting material **3a** has two sites available for protonation, namely, the keto and alcohol oxygen atoms. Preferential protonation of the keto group would result in Schiff base formation prior to nucleophilic attack on the propargylic alcohol moiety. However, the latter would be expected in the case that the alcohol oxygen atom is protonated first. Dehydration of the propargylic alcohol generates an allene cation which can be attacked by nucleophiles and eventually would deliver scrambled products similar to Meyer–Schuster[18] and Rupe[19] rearrangements. However, in our experiments, no such rearranged products have been observed which indicates that dehydration of the propargylic alcohol is not the first step. This is supported by the fact that keto-protonated isomer $\mathbf{Int_{1A}}$ is 2.85 kcal mol^{-1} more stable than the hydroxy-protonated isomer $\mathbf{Int_{1B}}$. Nucleophilic attack of urea on $\mathbf{Int_{1A}}$, followed by proton shift of $\mathbf{Int_{2A}}$ and subsequent dehydration, generates the Schiff base intermediate $\mathbf{Int_{3A}}$ *via* $\mathbf{Int_{2A}}$. The overall process is thermodynamically favourable by 6.74 kcal mol^{-1}. A proton shift from the imine nitrogen to the alcohol oxygen generates $\mathbf{Int_{4A}}$ in which the O–C

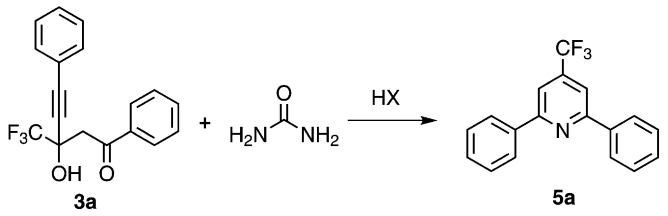


[a] Starting from **3n**.
[b] Starting from **3q**.

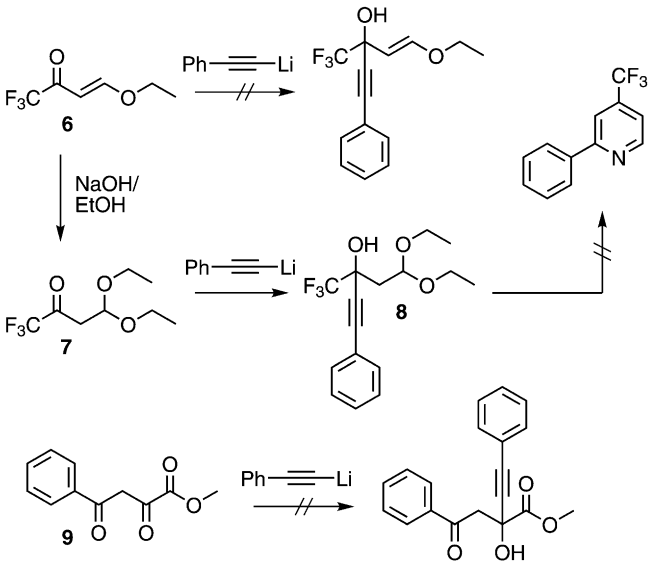
Figure 3. Scope of trifluoromethyl-substituted pyridines.

bond is considerably weak (3.11 Å) which indicates that the actual species participating in the next cyclization step is the dehydrated species $\mathbf{Int_{5A}}$ (Figur 5)

A transition state for the cyclization has been located at a barrier of 7.6 kcal mol^{-1}. Although the product of cyclization is a constrained molecule with an allene-like structure, the cyclization is thermodynamically favourable by 1.2 kcal mol^{-1}. A reason for the low barrier may be the instability of the bis-allene



Scheme 3. Synthesis of pyridine **5a**.



Scheme 4. Unsuccessful experiments.

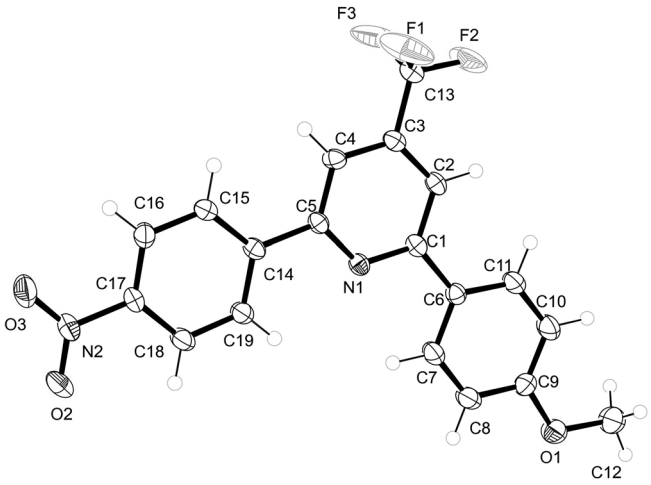


Figure 4. X-Ray structure of compound **5q**.

starting material $\mathbf{Int_{5A}}$. The cyclized product can undergo either an intramolecular 1,5 hydrogen shift or a deprotonation/protonation sequence to yield intermediate $\mathbf{Int_{7A}}$. The kinetic barrier for the sigmatropic 1,5 shift is more than 50 kcal mol^{-1} which renders this pathway inaccessible under the experimental conditions (refluxing toluene). Therefore, the more logical pathway follows a deprotonation/protonation mechanism which was previously demonstrated by theoretical and labelling studies.[20] The weak base (trifluoroacetate) abstracts a proton and transfers it to the central atom of the allene moiety.[21] The resulting intermediate undergoes hydrolysis to afford the pyridine (Figure 6). The water formed during the generation of $\mathbf{Int_{5A}}$ may participate in the hydrolysis. Adduct $\mathbf{Int_{8A}}$, which is generated by addition of water to $\mathbf{Int_{7A}}$, is thermodynamically less stable than its precursor (by 14.93 kcal mol^{-1}). A transition state ($\mathbf{TS_{8A}}$) has been located for the dissociation of carbamic acid from the pyridine moiety. The barrier is low (0.3 kcal mol^{-1}) and the cleavage is thermodynamically favourable (by 1.4 kcal mol^{-1}).

In conclusion, we have developed a new and convenient two-step procedure for the synthesis of 4-trifluoromethyl-substituted pyridines starting from 1,3-diketones, terminal alkynes and urea. A computational study on the mechanism was performed. The transformations are easy to handle and do not require costly reagents or catalysts.

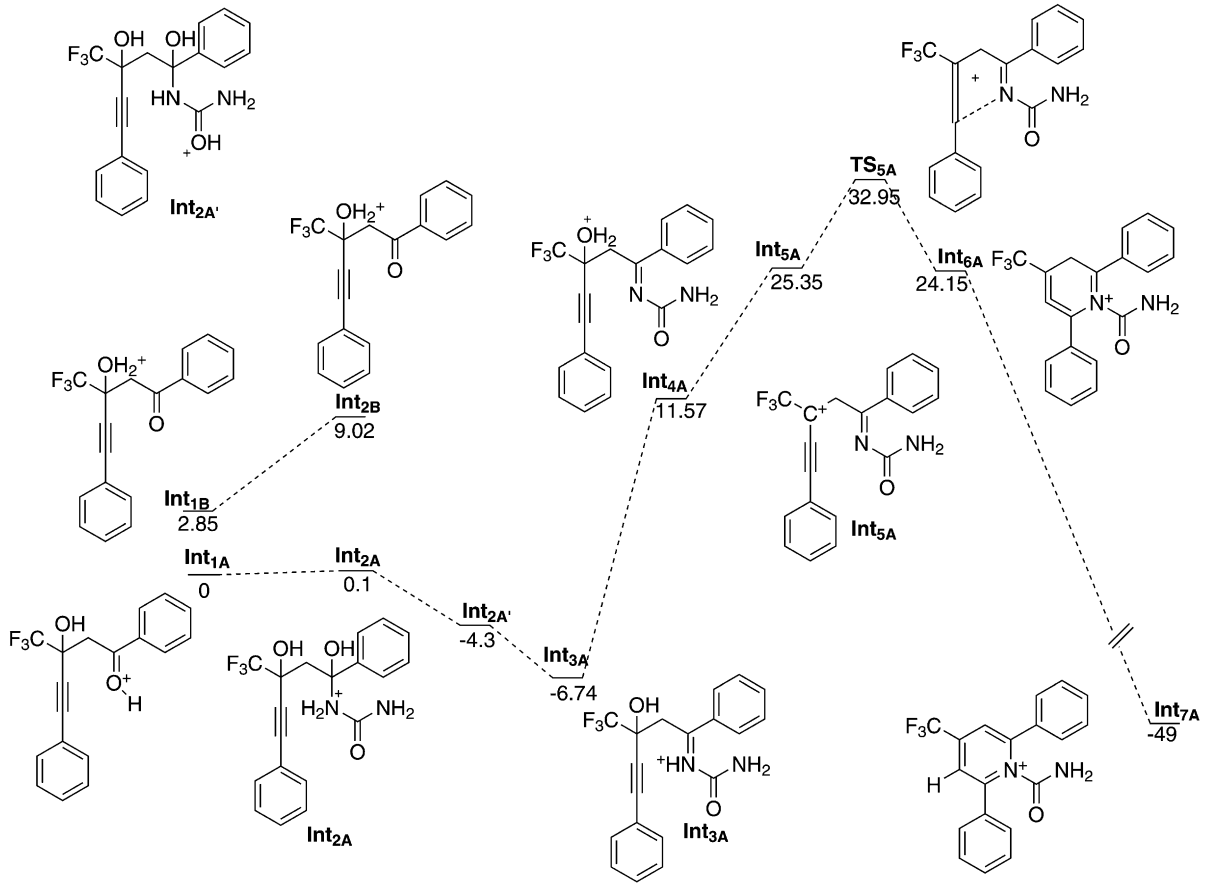


Figure 5. Energy profile for the acid-catalyzed pyridine formation. All values are in kcal mol^{-1} and include unscaled zero point energy correction.

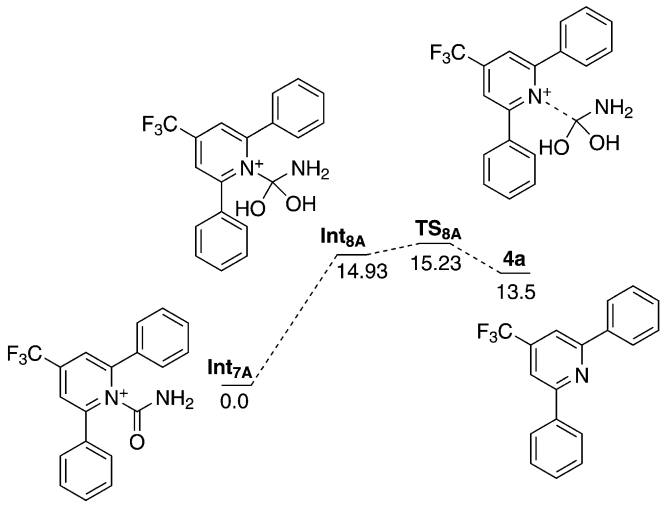


Figure 6. Hydrolysis of $\mathbf{Int_{7A}}$, All values are in kcal mol^{-1} and include unscaled zero point energy correction.

Experimental Section

General

All solvents were purified and dried by standard methods. NMR spectra were recorded on Brucker AVANCE 250 II and Brucker DPX 300 spectrometers. The following abbreviations are used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer FT-IR 1600 spectrometer (ATR). Mass spectra were obtained on a Hewlett–Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on a MX-1321 instrument (EI, 70 eV) by direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck 60F_{254} plates were used for TLC. The X-ray crystal structure analyses were deposited at the CCDC.[22]

General Procedure for the Synthesis of 3-Hydroxy-pent-4-yn-1-ones 3a–r

A Schlenk flask, containing a solution of terminal alkyne (0.0055 mol) in 6 mL of dry THF was cooled down to −78 °C and an equimolar amount of *n*-BuLi was added dropwise. After addition, the reaction mixture was allowed to warm up to room temperature during 1.5 h and was then cooled down again. The CF_3-derived diketone (0.0025 mol), dissolved in 2.5 mL of dry THF, was added dropwise to the mixture and the solution was warmed to 20 °C during 3 h. Afterwards, a solution of 0.0075 mol of NH_4Cl in 5 mL of water was added and the mixture was stirred during 15 min. The organic layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, washed with water and dried over Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography to give compounds **2**.

General Procedure for Preparation of 4-Trifluoromethylpyridine Compounds 5a–q

The 3-hydroxypent-4-yn-1-one (1.0 mmol) was dissolved in toluene (3.5 mL) and, subsequently, urea (72 mg, 1.2 mmol) and TFA (400 mg, 3.5 mmol) were added. The mixture was heated under reflux until full conversion of the starting material (monitored by TLC). Afterwards, triethylamine (0.404 mg, 0.004 mol) was added and the solution was concentrated under vacuum. The residue was purified by column chromatography to give the desired pyridines.

3-Hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (3a): Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and phenylacetylene (561 mg, 5.5 mmol); **3a** was isolated as light-yellow powder; yield: 604 mg (76%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.34 (d, 1H, H-2a, ^2J = 16.8 Hz), 3.70 (d, 1H, H-2b, ^2J = 16.8 Hz), 5.35 (s, 1H, OH), 7.17 (br. m, 5H, Ph), 7.43 (m, 2H, H-3′, H-5′), 7.55 (d, 1H, H-4′, ^3J = 7.5 Hz), 7.91 (dd, 2H, H-2′, H-6′, $^3J_1$ = 7.2 Hz, $^3J_2$ = 1.2 Hz); ^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 43.0 (C-2), 68.8 (q, C-3, $^2J_{C,F}$ = 31.5 Hz), 84.3 (C-4), 86.7 (C-5), 120.1 (C-4′), 124.1 (q, CF_3, $^1J_{C,F}$ = 286.2 Hz), 128.5 (C-2′, C-6′), 128.6 (C-3″, C-5″), 128.7 (C-3′, C-5′), 129.4 (C-1′), 131.4 (C-2″, C-6″), 133.2 (C-4″), 137.2 (C-1″), 194.5 (C-1); GC-MS (EI, 70 eV): *m/z* (%) = 318 (14) [M$^+$], 300 (15), 249 (48), 207 (41), 178 (25), 129 (76), 105 (100), 77 (68); HR-MS (ESI): *m/z* = 319.0945, [M+H]$^+$, calcd. for $C_{18}H_{14}F_3O_2$: 319.0940; IR (ATR): $\tilde{\nu}$ = 3398, 2955, 2222, 1622, 1599, 1575, 1512, 1453, 1403, 1167, 1045, 996, 832, 633 cm^{-1}.

5-(4-*tert*-Butylphenyl)-3-hydroxy-1-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (3b): Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and 4-*tert*-butylphenylacetylene (869 mg, 5.5 mmol); **3b** was isolated as light-yellow liquid; yield: 776 mg (83%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.19 (s, 9H, *t*-Bu), 3.34 (d, 1H, H-2a, ^2J = 16.8 Hz), 3.73 (d, 1H, H-2b, ^2J = 16.8 Hz), 5.37 (s, 1H, OH), 7.21 (br. s, 4H, H-2′, H-3′, H-5′, H-6′), 7.44 (m, 2H, H-3″, H-5″), 7.57 (m, 1H, H-4″), 7.92 (m, 2H, H-2″, H-6″); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 31.1 (CH_3), 34.8 [$(CH_3)_3C$], 41.7 (C-2), 70.6 (q, C-3, $^2J_{C,F}$ = 32.6 Hz), 82.7 (C-4), 87.0 (C-5), 118.0 (C-4′), 123.3 (q, CF_3, $^1J_{C,F}$ = 284.3 Hz), 125.3 (C-2′, C-6′), 128.4 (C-3′, C-5′), 128.9 (C-3″, C-5″), 131.7 (C-2″, C-6″), 134.4 (C-4″), 136.3 (C-1′), 152.6 (C-1″), 198.6 (C-1); GC-MS (EI, 70 eV): *m/z* (%) = 359 (49), 341 (60), 254 (21), 239 (100), 185 (35), 105 (76), 77 (56); HR-MS (ESI): *m/z* = 375.1563 [M+H]$^+$, calcd. for $C_{22}H_{22}F_3O_2$: 375.1566; IR (ATR): $\tilde{\nu}$ = 3327, 2983, 2230, 1670, 1578, 1576, 1497, 1469, 1447, 1211, 1039, 843, 779, 765 cm^{-1}.

3-Hydroxy-1-phenyl-3-(trifluoromethyl)non-4-yn-1-one (3c): Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and 1-hexyne (451 mg, 5.5 mmol); **3c** was isolated as colorless liquid; yield: 529 mg (71%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.76 (t, 3H, CH_3, ^3J = 7.2 Hz), 1.30 (m, 4H, CH_2), 2.08 (t, 2H, CH_2, ^3J = 7.2 Hz), 3.30 (d, 1H, H-2a, ^2J = 16.2 Hz), 3.60 (d, 1H, H-2b, ^2J = 16.2 Hz), 5.20 (s, 1H, OH), 7.55 (br. m, 3H, H-2′, H-4′, H-6′), 7.90 (dd, 2H, H-3′, H-5′, $^3J_1$ = 5.1 Hz, $^3J_2$ = 0.9 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.4 (C-9), 18.2 (C-8), 21.7 (C-7), 30.0 (C-6), 41.7 (C-2), 70.2 (q, C-3, $^2J_{C,F}$ = 32.1 Hz), 75.0 (C-4), 88.3 (C-5), 123.3 (q, CF_3, $^1J_{C,F}$ = 283.7 Hz), 128.4 (C-3′, C-5′), 128.9 (C-2′, C-6′), 134.3 (C-4′), 136.4 (C-1′), 198.7 (C-1); GC-MS (EI, 70 eV): *m/z* (%) = 256 (10), 187 (10), 105 (100), 77 (46);

HR-MS (ESI): $m/z = 299.1247$ $[M+H]^+$, calcd. for $C_{16}H_{18}F_3O_2$: 299.1253; IR (ATR): $\tilde{\nu} = 3217, 2219, 1658, 1529, 1456, 1389, 1286, 1214, 1000, 922, 866, 786, 619\ cm^{-1}$.

3-Hydroxy-1-phenyl-3-(trifluoromethyl)tridec-4-yn-1-one (3d): Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and 1-decyne (759 mg, 5.5 mmol); **3d** was isolated as a colourless liquid; yield: 593 mg (67%); ^1H NMR (250.13 MHz, $CDCl_3$): $\delta = 0.76$ (t, 3H, CH_3, $^3J = 7.5$ Hz), 1.29 (m, 12H, CH_2), 2.07 (t, 2H, CH_2, $^3J = 7.0$ Hz), 3.23 (d, 1H, H-2a, $^2J = 16.8$ Hz), 3.60 (d, 1H, H-2b, $^2J = 16.8$ Hz), 5.21 (s, 1H, -OH), 7.47 (br. m, 3H, H-2′, H-4′, H-6′), 7.91 (dd, 2H, H-3′, H-5′, $^3J_1 = 1.5$ Hz, $^3J_2 = 1.0$ Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): $\delta = 14.0$ (C-13), 18.5 (C-12), 22.6 (C-11), 27.9 (C-10), 28.6 (C-9), 28.9 (C-8), 29.0 (C-7), 31.8 (C-6), 41.7 (C-2), 70.1 (q, C-3, $^2J_{C,F} = 32.7$ Hz), 75.0 (C-4), 88.3 (C-5), 123.3 (q, CF_3, $^1J_{C,F} = 283.1$ Hz), 128.4 (C-3′, C-5′), 128.9 (C-2′, C-6′), 134.3 (C-4′), 136.6 (C-1′), 198.7 (C-1); GC-MS (EI, 70 eV): m/z (%) = 285 (10), 238 (10), 105 (100), 77 (44); HR-MS (ESI): $m/z = 355.1880$ $[M+H]^+$, calcd. for $C_{20}H_{26}F_3O_2$: 355.1879; IR (ATR): $\tilde{\nu} = 3437, 2925, 2855, 2240, 1674, 1597, 1450, 1348, 1173, 1002, 755, 686, 624\ cm^{-1}$.

3-Hydroxy-5-phenyl-1-(thiophen-2-yl)-3-(trifluoromethyl)-pent-4-yn-1-one (3e): Starting from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (555 mg, 2.5 mmol) and phenylacetylene (561 mg, 5.5 mmol); **3e** was isolated as light-grey powder; yield: 656 mg (81%); ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.32$ (d, 1H, H-2a, $^2J = 16.5$ Hz), 3.61 (d, 1H, H-2b, $^2J = 16.5$ Hz), 5.34 (s, 1H, -OH), 7.26 (br. m, 6H, H-2′, H-4′, H-6′, H-3″, H-4″, H-5″), 7.75 (m, 2H, H-3′, H-5′); ^{13}C NMR (62.90 MHz, $CDCl_3$): $\delta = 42.4$ (C-2), 70.6 (q, C-3, $^2J_{C,F} = 32.7$ Hz), 83.1 (C-4), 87.1 (C-5), 123.2 (q, CF_3, $^1J_{C,F} = 283.7$ Hz), 128.3 (C-2′, C-6′), 128.6 (C-4′), 129.3 (C-4″), 131.8 (C-1′), 132.0 (C-3′, C-5′), 134.0 (C-3″), 136.1 (C-5″), 143.3 (C-2″), 190.7 (C-1); GC-MS (EI, 70 eV): m/z (%) = 323 (21) $[M-H^+]$, 255 (23), 237 (18), 184 (43), 129 (99), 111 (100); HR-MS (ESI): $m/z = 325.0508$ $[M+H]^+$, calcd. for $C_{16}H_{12}F_3O_2S$: 325.0505; IR (ATR): $\tilde{\nu} = 3297, 2918, 2229, 1661, 1587, 1522, 1496, 1423, 1398, 1233, 1098, 1010, 954, 812\ cm^{-1}$.

3-Hydroxy-5-(4-methoxyphenyl)-1-(thiophen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (3f): Starting from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (555 mg, 2.5 mmol) and 4-methoxyphenylacetylene (726 mg, 5.5 mmol); **3f** was isolated as light-yellow powder; yield: 708 mg (80%); ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.30$ (d, 1H, H-2a, $^2J = 16.5$ Hz), 3.58 (d, 1H, H-2b, $^2J = 16.5$ Hz), 3.71 (s, 3H, OCH_3), 5.29 (s, 1H, OH), 6.71 (d, 2H, H-2′, H-6′, $^3J = 4.8$ Hz), 7.19 (m, 3H, H-3′, H-5′, H-4), 7.47 (m, 2H, H-3″, H-5″); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 42.5$ (OCH_3), 55.3 (C-2), 70.7 (q, C-3, $^2J_{C,F} = 32.5$ Hz), 81.9 (C-4), 87.3 (C-5), 113.0 (C-4"), 113.9 (C-2′, C-6′), 122.9 (q, CF_3, $^1J_{C,F} = 283.7$ Hz), 128.9 (C-3″), 133.1 (C-3′, C-5′), 134.0 (C-4″), 136.0 (C-5″), 143.4 (C-2″), 160.3 (C-1′), 190.8 (C-1); GC-MS (EI, 70 eV): m/z (%) = 428 (93), 409 (11), 228 (100), 214 (23), 200 (71); HR-MS (ESI): $m/z = 355.0163$ $[M+H]^+$, calcd for $C_{17}H_{14}F_3O_3S$: 355.0160; IR (ATR): $\tilde{\nu} = 3350, 3018, 2897, 1653, 1598, 1524, 1447, 1229, 1210, 1143, 1018, 859, 687\ cm^{-1}$.

3-Hydroxy-1-(thiophen-2-yl)-3-(trifluoromethyl)dec-4-yn-1-one (3g): Starting from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (555 mg, 2.5 mmol) and 1-heptyne (528 mg, 5.5 mmol); **3g** was isolated as a yellow liquid; yield: 485 mg (61%); ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 0.83$ (t, 3H, CH_3, $^3J = 2.4$ Hz), 1.17 (br. m, 6H, CH_2), 2.08 (t, 2H, CH_2, $^3J = 6.9$ Hz), 3.18 (d, 1H, H-2a, $^2J = 15.9$ Hz), 3.48 (d, 1H, H-2b, $^2J = 15.9$ Hz), 5.17 (s, 1H, OH), 7.13 (m, 1H, H-4′), 7.71 (m, 2H, H-3′, H-5′); ^{13}C NMR (62.90 MHz, $CDCl_3$): $\delta = 13.8$ (C-10), 18.4 (C-9), 22.0 (C-8), 27.6 (C-7), 30.7 (C-6), 42.4 (C-2), 70.1 (q, C-3, $^2J_{C,F} = 32.1$ Hz), 74.7 (C-4), 88.6 (C-5), 123.2 (q, CF_3, $^1J_{C,F} = 283.7$ Hz), 128.6 (C-4′), 133.9 (C-3′), 135.9 (C-5′), 143.4 (C-2′), 191.0 (C-1); GC-MS (EI, 70 eV): m/z (%) = 257 (31), 244 (100), 231 (24), 216 (12), 189 (10), 147 (13), 111 (21). HRMS (ESI): $m/z = 319.0972$ $[M+H]^+$, calcd. for $C_{15}H_{18}F_3O_2S$: 319.0974; IR (ATR): $\tilde{\nu} = 3405, 2840, 2233, 1645, 1605, 1509, 1411, 1243, 1168, 1072, 831, 726, 628\ cm^{-1}$.

3-Hydroxy-1-(thiophen-2-yl)-3-(trifluoromethyl)undeca-4,10-diyn-1-one (3h): Starting from 4,4,4-trifluoro-1-(thiophen-2-yl)butane-1,3-dione (555 mg, 2.5 mmol) and 1,7-octadiyne (583 mg, 5.5 mmol); **3h** was isolated as a yellow liquid; yield: 0.517 g (63%); ^1H NMR (250.13 MHz, $CDCl_3$): $\delta = 1.46$ (m, 4H, CH_2), 1.85 (t, 1H, H-11, $^3J = 3.0$ Hz), 2.06 (m, 4H, CH_2), 3.19 (d, 1H, H-2a, $^2J = 19.2$ Hz), 3.48 (d, 1H, H-2b, $^2J = 19.2$ Hz), 5.20 (s, 1H, OH), 7.13 (dd, 1H, H-4′, $^3J_1 = 3.6$ Hz, $^3J_2 = 1.2$ Hz), 7.20 (m, 2H, H-3′, H-5′); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 17.8$ (C-8), 18.0 (C-7), 26.8 (C-9), 27.2 (C-6), 42.4 (C-2), 68.6 (C-11), 70.1 (q, C-3, $^2J_{C,F} = 32.5$ Hz), 75.2 (C-10), 83.9 (C-4), 88.0 (C-5), 123.2 (q, CF_3, $^1J_{C,F} = 283.8$ Hz), 128.6 (C-4′), 133.9 (C-3′), 136.0 (C-5′), 143.4 (C-2′), 190.9 (C-1); GC-MS (EI, 70 eV): m/z (%) = 302 (14), 243 (43), 202 (28), 144 (100), 128 (19); HR-MS (ESI): $m/z = 329.0782$ $[M+H]^+$, calcd. for $C_{16}H_{16}F_3O_2S$: 329.0786; IR (ATR): $\tilde{\nu} = 3369, 3288, 2237, 2196, 1629, 1587, 1506, 1468, 1387, 1241, 1176, 1033, 954, 814, 682\ cm^{-1}$.

1-(Furan-2-yl)-3-hydroxy-5-(4-methoxyphenyl)-3-(trifluoromethyl)pent-4-yn-1-one (3i): Starting from 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (515 mg, 2.5 mmol) and 4-methoxyphenylacetylene (726 mg, 5.5 mmol); **3i** was isolated as light-yellow flakes; yield: 566 mg (67%); ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 3.23$ (d, 1H, H-2a, $^2J = 16.2$ Hz), 3.56 (d, 1H, H-2b, $^2J = 16.2$ Hz), 3.71 (s, 3H, OCH_3), 5.17 (s, 1H, OH), 6.54 (dd, 1H, H-4″, $^3J_1 = 1.8$ Hz, $^3J_2 = 1.8$ Hz), 6.72 (m, 2H, H-2′, H-6′), 7.24 (m, 3H, H-3′, H-5′, H-3″), 7.60 (d, 1H, H-5″, $^3J = 0.9$ Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta =$ 41.7 (OCH_3), 55.3 (C-2), 70.6 (q, C-3, $^2J_{C,F} = 32.5$ Hz), 81.8 (C-4), 87.2 (C-5), 113.1 (C-4″), 113.9 (C-2′, C-6′), 119.5 (C-3″), 123.3 (q, CF_3, $^1J_{C,F} = 284.5$ Hz), 133.1 (C-3′, C-5′), 148.0 (C-4′), 152.1 (C-1″), 160.3 (C-1′), 186.4 (C-1); GC-MS (EI, 70 eV): m/z (%) = 338 (18) $[M^+]$, 228 (15), 198 (11), 159 (100), 144 (17), 95 (52); HR-MS (ESI): $m/z = 338.0761$ $[M]^+$, calcd. for $C_{17}H_{13}F_3O_4$: 338.0760; IR (ATR): $\tilde{\nu} = 3386, 2964, 2198, 1673, 1575, 1524, 1497, 1446, 1389, 1221, 1075, 849, 712\ cm^{-1}$.

1-(Furan-2-yl)-3-hydroxy-3-(trifluoromethyl)dec-4-yn-1-one (3j): Starting from 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (515 mg, 2.5 mmol) and 1-heptyne (528 mg, 5.5 mmol); **3j** was isolated as an orange liquid; yield: 461 mg (61%); ^1H NMR (300.13 MHz, $CDCl_3$): $\delta = 0.78$ (t, 3H, CH_3, $^3J = 2.1$ Hz), 1.21 (br. m, 6H, CH_2), 2.08 (t, 2H, CH_2, $^3J = 6.6$ Hz), 3.11 (d, 1H, H-2a, $^2J = 16.2$ Hz), 3.45 (d, 1H, H-2b, $^2J = 16.2$ Hz), 5.05 (s, 1H, OH), 6.55 (dd, 1H, H-4′, $^3J_1 = 2.1$ Hz, $^3J_2 = 2.1$ Hz), 7.27 (dd, 1H, H-3′, $^3J_1 = 3.3$ Hz, $^3J_2 = 0.4$ Hz), 7.60 (t, 1H, H-5′, $^3J = 0.6$ Hz); ^{13}C NMR (75.47 MHz, $CDCl_3$): $\delta = 13.8$ (C-10), 18.4 (C-9), 22.0 (C-8), 27.6 (C-7), 30.7 (C-6), 41.6 (C-2), 70.0 (q, C-3, $^2J_{C,F} =$

32.5 Hz), 74.5 (C-4), 88.6 (C-5), 113.0 (C-4′), 119.4 (C-3′), 123.2 (q, CF_3, $^1J_{C,F}$=284.5 Hz), 147.9 (C-5′), 152.1 (C-1′), 186.6 (C-1); GC-MS (EI, 70 eV): *m/z* (%)=274 (100), 144 (11), 44 (14); HR-MS (ESI): *m/z*=303.1198 $[M+H]^+$, calcd. for $C_{15}H_{18}F_3O_3$: 303.1203; IR (ATR): $\tilde{\nu}$=3424, 2933, 2242, 1658, 1569, 1465, 1175, 1100, 1004, 883, 765, 653 cm^{-1}.

3-Hydroxy-1-(naphthalen-2-yl)-5-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (3k): Starting from 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione (665 mg, 2.5 mmol) and phenylacetylene (561 mg, 5.5 mmol); **3k** was isolated as a light-yellow powder; yield: 0.681 g (74%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=3.48 (d, 1H, H-2a, ^2J=16.5 Hz), 3.87 (d, 1H, H-2b, ^2J=16.5 Hz), 5.49 (s, 1H, OH), 7.18 (br. m, 5H, Ph), 7.55 (m, 2H, H-5′, H-7′), 7.91 (br. m, 4H, H-3′, H-4′, H-6′, H-8′), 8.43 (s, 1H, H-1′); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=41.7 (C-2), 70.7 (q, C-3, $^2J_{C,F}$=32.5 Hz), 83.4 (C-4), 86.9 (C-5), 123.4 (q, CF_3, $^1J_{C,F}$=284.5 Hz), 123.4 (C-5″), 127.2 (C-7″), 127.9 (C-8″), 128.3 (C-3′, C-5′), 129.0 (C-6″), 129.2 (C-4″), 129.3 (C-3″), 129.8 (C-1″), 130.9 (C-4′), 131.9 (C-1′), 132.0 (C-2′, C-6′), 132.4 (C-8a″), 133.6 (C-4a″), 136.2 (C-2″), 198.4 (C-1); GC-MS (EI, 70 eV): *m/z* (%)=368 (55) $[M^+]$, 350 (20), 299 (24), 281 (26), 228 (56), 170 (36), 155 (98), 127 (100), 101 (15); HR-MS (ESI): *m/z*=368.1019 $[M]^+$, calcd. for $C_{22}H_{15}F_3O_2$: 368.1019; IR (ATR): $\tilde{\nu}$=3399, 3077, 2223, 1678, 1597, 1464, 1431, 1229, 1163, 1055, 987, 963, 879, 787, 679 cm^{-1}.

5-(3-Fluorophenyl)-3-hydroxy-1-(naphthalen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (3lL): Starting from 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione (665 mg, 2.5 mmol) and 3-fluorophenylacetylene (660 mg, 5.5 mmol); **3l** was isolated as a light-yellow powder; yield: 676 mg (70%); ^{1}H NMR (500.13 MHz, CD_2Cl_2): δ=3.47 (d, 1H, H-2a, ^2J=16.5 Hz), 3.87 (d, 1H, H-2b, ^2J=16.5 Hz), 5.46 (s, 1H, OH), 6.94 (m, 2H, H-2′, H-4′), 7.05 (m, 1H, H-6′), 7.13 (dd, 1H, H-5′, $^3J_1$=5.5 Hz, $^3J_2$=1.0 Hz), 7.49 (dd, 1H, H-6″, $^3J_1$=7.0 Hz, $^3J_2$=1.0 Hz), 7.55 (dd, 1H, H-7″, $^3J_1$=7.0 Hz, $^3J_2$=1.0 Hz), 7.85 (br. m, 4H, H-3″, H-4″, H-5″, H-8″), 8.42 (d, 1H, H-1″, ^3J=1.0 Hz); ^{13}C NMR (125.76 MHz, CD_2Cl_2): δ=42.1 (C-2), 71.0 (q, C-3, $^2J_{C,F}$=32.7 Hz), 84.8 (C-4), 85.7 (d, C-5, $^4J_{C,F}$=3.8 Hz), 117.0 (d, C-2′, $^2J_{C,F}$=23.9 Hz), 119.0 (d, C-4′, $^2J_{C,F}$=23.9 Hz), 123.2 (q, CF_3, $^1J_{C,F}$=284.1 Hz), 123.7 (C-6′), 127.7 (C-5″), 128.3 (d, 1H, C-4′, $^3J_{C,F}$=7.6 Hz), 129.0 (C-7″), 129.3 (C-6″), 129.6 (C-8″), 130.2 (C-4″), 130.5 (C-3″), 131.0 (C-4a″, C-8a″), 131.3 (C-1″), 132.8 (d, C-1′, $^3J_{C,F}$=8.8 Hz), 136.6 (C-2″), 162.5 (d, C-3′, $^1J_{C,F}$=246.9 Hz), 198.7 (C-1); GC-MS (EI, 70 eV): *m/z* (%)=368 (100), 299 (38), 270 (59), 246 (21), 220 (22), 152 (53), 144 (25), 127 (66); HRMS (ESI): *m/z*=386.0927 $[M]^+$, calcd. for $C_{22}H_{14}F_4O_2$: 386.0924; IR (ATR): $\tilde{\nu}$=3457, 3077, 2229, 2201, 1674, 1580, 1485, 1470, 1435, 1367, 1339, 1233, 1163, 1070, 955, 933, 860, 832, 777, 741, 673, 561 cm^{-1}.

3-Hydroxy-1-(naphthalen-2-yl)-3-(trifluoromethyl)dec-4-yn-1-one (3m): Starting from 4,4,4-trifluoro-1-(naphthalen-2-yl)butane-1,3-dione (665 mg, 2.5 mmol) and 1-heptyne (528 mg, 5.5 mmol); **3m** was isolated as a colorless liquid; yield: 579 mg (64%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=0.70 (t, 3H, CH_3, ^3J=2.4 Hz), 1.16 (br. m, 6H, CH_2), 2.06 (t, 2H, CH_2, ^3J=6.9 Hz), 3.35 (d, 1H, H-2a, ^2J=16.5 Hz), 3.75 (d, 1H, H-2b, ^2J=16.5 Hz), 5.30 (s, 1H, OH), 7.55 (m, 2H, H-5′, H-7′), 7.88 (br. m, 4H, H-3′, H-4′, H-6′, H-8′), 8.41 (s, 1H, H-1′); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ=13.8 (C-10), 18.5 (C-9), 22.0 (C-8), 27.6 (C-7), 30.7 (C-6), 41.7 (C-2), 70.3 (q, C-3, $^2J_{C,F}$=32.7 Hz), 75.0 (C-4), 88.4 (C-5), 123.3 (q, CF_3, $^1J_{C,F}$=283.7 Hz), 123.4 (C-5′), 127.2 (C-7′), 127.9 (C-8′), 128.8 (C-6′), 129.2 (C-4′), 129.8 (C-3′), 130.1 (C-1′), 132.3 (C-8a′), 133.7 (C-4a′), 136.1 (C-2′), 198.6 (C-1); GC-MS (EI, 70 eV): *m/z* (%)=345 (15), 288 (12), 170 (32), 155 (100), 127 (94); HR-MS (ESI): *m/z*=362.1483 $[M]^+$, calcd. for $C_{21}H_{21}F_3O_2$: 362.1488; IR (ATR): $\tilde{\nu}$=3437, 2930, 2238, 1667, 1469, 1356, 1242, 1171, 1100, 822, 746, 671 cm^{-1}.

3-Hydroxy-5-phenyl-1-(pyridin-2-yl)-3-(trifluoromethyl)-pent-4-yn-1-one (3n): Starting from 4,4,4-trifluoro-1-(pyridin-2-yl)butane-1,3-dione (543 mg, 2.5 mmol) and phenylacetylene (561 mg, 5.5 mmol); **3n** was isolated as a violet liquid; yield: 502 mg (63%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=3.61 (d, 1H, H-2a, ^2J=14.4 Hz), 3.71 (d, 1H, H-2b, ^2J=14.4 Hz), 7.23 (br. m, 5H, Ph), 7.53 (m, 1H, H-5′), 7.90 (m, 1H, H-3″), 8.10 (m, 1H, H-4′), 8.63 (s, 1H, H-6′); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ=46.5 (C-2), 69.7 (q, C-3, $^2J_{C,F}$=32.7 Hz), 83.4 (C-4), 87.3 (C-5), 121.2 (C-1′), 123.2 (C-5″) 123.7 (q, CF_3, $^1J_{C,F}$=284.9 Hz), 128.0 (C-4′), 128.2 (C-2′, C-6′), 129.1 (C-3″), 132.0 (C-3′, C-5′), 138.3 (C-4″), 148.2 (C-6″), 152.1 (C-2″), 196.0 (C-1); GC-MS (EI, 70 eV): *m/z* (%)=319 (11) $[M^+]$, 250 (18), 222 (17), 198 (11), 129 (100), 121 (21), 78 (29); HR-MS (ESI): *m/z*=319.0816 $[M]^+$, calcd, for $C_{17}H_{12}F_3NO_2$: 319.0815; IR (ATR): $\tilde{\nu}$=3414, 2876, 2234, 1700, 1596, 1579, 1512, 1498, 1287, 1153, 1012, 913, 846, 655 cm^{-1}.

3-Hydroxy-5-(4-methoxyphenyl)-1-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (3o): Starting from 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (543 mg, 2.5 mmol) and 4-methoxyphenylacetylene (726 mg, 5.5 mmol); **3o** was isolated as a light-green liquid; yield: 497 mg (59%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=3.54 (d, 1H, H-2a, ^2J=14.1 Hz), 3.66 (d, 1H, H-2b, ^2J=14.1 Hz), 3.69 (s, 3H, OCH_3), 6.72 (m, 2H, H-2′, H-6′), 7.20 (m, 2H, H-3′, H-5′), 7.53 (m,1H, H-5″), 7.89 (m, 2H, H-3″, OH), 8.06 (m, 1H, H-4″), 8.61 (m, 1H, H-6″); ^{13}C NMR (62.90 MHz, CD_2Cl_2): δ=47.0 (C-2), 55.7 (-OCH_3), 70.0 (q, C-3, $^2J_{C,F}$=32.7 Hz), 82.7 (C-4), 87.6 (C-5), 113.4 (C-4′), 114.3 (C-2′, C-6′), 123.4 (C-5″), 124.2 (q, CF_3, $^1J_{C,F}$=284.9 Hz), 128.5 (C-3″), 133.7 (C-3′, C-5′), 138.8 (C-4″), 148.7 (C-6″), 152.6 (C-2″), 160.8 (C-1′), 196.4 (C-1); GC-MS (EI, 70 eV): *m/z* (%)=228 (28), 159 (100), 144 (20), 116 (18), 88 (14); HR-MS (ESI): *m/z*=350.0993 $[M+H]^+$, calcd. for $C_{18}H_{15}F_3NO_3$: 350.0999; IR (ATR): $\tilde{\nu}$=3391, 2935, 2840, 2232, 1698, 1605, 1509, 1247, 1169, 1107, 1027, 832, 617 cm^{-1}.

6-Cyclohexyl-3-hydroxy-1-(pyridin-2-yl)-3-(trifluoromethyl)hex-4-yn-1-one (3p): Starting from 4,4,4-trifluoro-1-(furan-2-yl)butane-1,3-dione (543 mg, 2.5 mmol) and 3-cyclohexyl-prop-1-yne (671 mg, 5.5 mmol); **3p** was isolated as a light-violet liquid; yield: 483 mg (57%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=0.81 (br.m, 6H, Cy), 1.04 (m, 5H, Cy), 1.95 (d, 2H, H-6, ^3J=5.4 Hz), 3.51 (d, 1H, H-2a, ^2J=15.3 Hz), 3.55 (d, 1H, H-2b, ^2J=15.3 Hz), 7.52 (m, 1H, H-5′), 7.90 (m, 1H, H-3″), 8.08 (m, 1H, H-4′), 8.62 (m, 1H, H-6′); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ=26.1 (CH_2), 26.2 (CH_2), 32.3 (CH_2), 36.8 (CH), 46.6 (C-6), 68.8 (q, C-3, $^2J_{C,F}$=32.7 Hz), 75.8 (C-4), 87.7 (C-5), 123.3 (C-3′), 124.6 (q, CF_3, $^1J_{C,F}$=284.3 Hz), 127.3 (C-5′), 138.2 (C-4′), 148.2 (C-6′), 152.2 (C-2′), 196.3 (C-1); GC-MS (EI, 70 eV): *m/z* (%)=338 (14) $[M-H^+]$, 310 (16), 256 (46), 188 (35), 149 (29), 121 (80), 83 (100); HR-MS (ESI): *m/z*=340.1524, $[M+H]^+$,

calcd. for $C_{18}H_{21}F_3NO_2$: 340.1519; IR (ATR): $\tilde{\nu}$ = 2923, 2851, 2240, 1699, 1587, 1449, 1262, 1173, 1104, 617 cm^{-1}.

3-Hydroxy-1-phenyl-5-(pyridin-2-yl)-3-(trifluoromethyl)-pent-4-yn-1-one (3q): Starting from 3-benzoyl-1,1,1-trifluoroacetone (540 mg, 2.5 mmol) and 2-ethynylpyridine (567 mg, 5.5 mmol); **3q** was isolated as a dark-green powder; yield: 383 mg (48%); ^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 3.57 (d, 1H, H-2a, ^2J = 18.0 Hz), 3.87 (d, 1H, H-2b, ^2J = 18.0 Hz), 5.78 (s, 1H, OH), 7.59 (br. m, 6H, H-3′, H-4′, H-5′, H-2″, H-4″, H-6″), 8.04 (dd, 2H, H-3″, H-5″, $^3J_1$ = 3.6 Hz, $^3J_2$ = 3.0 Hz), 8.58 (m, 1H, H-6′); ^{13}C NMR (62.90 MHz, CD_2Cl_2): δ = 42.3 (C-2), 70.7 (q, C-3, $^2J_{C,F}$ = 32.7 Hz), 83.3 (C-4), 86.1 (C-5), 123.8 (q, CF_3, $^1J_{C,F}$ = 284.3 Hz), 123.9 (C-3′), 124.2 (C-5′), 128.0 (C-4″), 128.8 (C-2″, C-6″), 129.3 (C-3″, C-5″), 134.7 (C-4′), 136.6 (C-6′), 141.8 (C-1″), 150.4 (C-1″), 198.2 (C-1); GC-MS (EI, 70 eV): *m/z* (%) = 318 (46) [M−H$^+$], 250 (14), 222 (18), 180 (51), 130 (44), 105 (100), 77 (69); HRMS (ESI): *m/z* = 320.0890, [M+H]$^+$, calcd. for $C_{17}H_{13}F_3NO_2$: 320.0893; IR (ATR): $\tilde{\nu}$ = 3086, 2790, 2239, 1689, 1586, 1470, 1430, 1371, 1268, 1167, 1114, 1084, 976, 763, 688, 623 cm^{-1}.

3-Hydroxy-5-(4-methoxyphenyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)pent-4-yn-1-one (3r): Starting from 3-(4-nitrobenzoyl)-1,1,1-trifluoroacetone (653 mg, 2.5 mmol) and 4-methoxyphenylacetylene (726 mg, 5.5 mmol); **3r** was isolated as a yellow gum; yield: 609 mg (62%); ^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 3.46 (d, 1H, H-2a, ^2J = 15.2 Hz), 3.70 (s, 3H, OCH_3), 3.73 (d, 1H, H-2b, ^2J = 15.2 Hz), 4.66 (s, 1H, OH), 6.74 (dd, 2H, H-2′, H-6″, $^3J_1$ = 4.5 Hz, $^3J_2$ = 2.1 Hz), 7.22 (dd, 2H, H-3′, H-5′, $^3J_1$ = 4.5 Hz, $^3J_2$ = 2.1 Hz), 8.08 (dd, 2H, H-3″, H-5″, $^3J_1$ = 4.8 Hz, $^3J_2$ = 2.1 Hz), 8.27 (dd, 2H, H-2″, H-6″, $^3J_1$ = 4.8 Hz, $^3J_2$ = 2.1 Hz); ^{13}C NMR (62.90 MHz, CD_2Cl_2): δ = 43.2 (C-2), 55.6 (OCH_3), 70.5 (q, C-3, $^2J_{C,F}$ = 32.7 Hz), 81.8 (C-4), 87.8 (C-5), 114.3 (C-2′, C-6′), 123.4 (q, CF_3, $^1J_{C,F}$ = 284.9 Hz), 124.1 (C-3′, C-5′), 129.8 (C-3″, C-5″), 133.7 (C-2″, C-6″), 135.8 (C-1′), 141.0 (C-4″), 151.2 (C-1′), 160.9 (C-1″), 196.8 (C-1); GC-MS (EI, 70 eV): *m/z* (%) = 281 (78), 253 (20), 159 (100); HR-MS (ESI): *m/z* = 394.0892 [M+H]$^+$, calcd. for $C_{19}H_{15}F_3NO_5$: 394.0897; IR (ATR): $\tilde{\nu}$ = 3489, 3110, 2912, 2235, 1683, 1603, 1511, 1401, 1344, 1230, 1178, 1077, 1030, 947, 840, 747, 688, 639 cm^{-1}.

2,6-Diphenyl-4-(trifluoromethyl)pyridine (5a): Starting from 3-hydroxy-1,5-diphenyl-3-(trifluoromethyl)pent-4-yn-1-one (318 mg, 1 mmol) (**3a**) and urea (72 mg, 1.2 mmol); **5a** was isolated as a light-yellow powder; yield: 203 mg (68%); mp 62–64 °C; ^{1}H NMR (250.13 MHz, DMSO-d_6): δ = 7.49 (m, 6H, H-3′, H-4′, H-5′, H-3″, H-4″, H-5″), 8.25 (m, 6H, H-3, H-5, H-2′, H-6′, H-2″, H-6″); ^{13}C NMR (62.90 MHz, DMSO-d_6): δ = 112.6 (q, C-3, C-5, $^3J_{C,F}$ = 3.1 Hz), 121.6 (q, CF_3, $^1J_{C,F}$ = 274.2 Hz), 125.5 (C-3′, C-5′, C-3″, C-5″), 127.4 (C-2′, C-6′, C-2″, C-6″), 128.5 (C-4′, C-4″), 135.8 (C-1′, C-1″), 137.7 (q, C-4, $^2J_{C,F}$ = 33.3 Hz), 155.8 (C-2, C-6); GC-MS (EI, 70 eV): *m/z* (%) = 299 (100) [M$^+$], 230 (11), HR-MS (ESI): *m/z* = 300.0992 [M+H]$^+$, calcd. for $C_{18}H_{13}F_3N$: 300.0995; IR (ATR): $\tilde{\nu}$ = 2890, 1589, 1566, 1518, 1466, 1376, 1255, 1180, 1162, 1084, 877, 696 cm^{-1}.

2-(4-*tert*-Butylphenyl)-6-phenyl-4-(trifluoromethyl)pyridine (5b). Starting from 5-(4-*tert*-butylphenyl)-3-hydroxy-1-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (374 mg, 1 mmol) (**3b**) and urea (72 mg, 1.2 mmol); **5b** was isolated as a light-yellow liquid; yield: 216 mg (61%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.30 (s, 9H, *t*-Bu), 7.46 (br. m, 5H, Ph), 7.77 (s, 2H, H-3, H-5), 8.08 (br, m, 4H, H-2″, H-3″, H-5″, H-6″); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 31.3 (CH_3), 34.8 [$(CH_3)_3C$], 113.6 (d, C-5, $^3J_{C,F}$ = 3.8 Hz), 113.8 (d, C-3, $^3J_{C,F}$ = 3.8 Hz), 122.9 (q, CF_3, $^1J_{C,F}$ = 273.2 Hz), 125.9 (C-3″, C-5″), 126.9 (C-2′, C-6′), 127.1 (C-3′, C-5′), 128.9 (C-2″, C-6″), 129.8 (C-4″), 135.5 (C-1′), 138.3 (C-1″), 139.9 (q, C-4, $^2J_{C,F}$ = 34.0 Hz), 153.1 (C-4′), 158.1 (C-6), 158.3 (C-2); GC-MS (EI, 70 eV): *m/z* (%) = 355 (42) [M$^+$], 340 (100), 312 (14), 156 (20); HR-MS (ESI): *m/z* = 355.1537 [M]$^+$, calcd. for $C_{20}H_{20}F_3N$: 355.1542; IR (ATR): $\tilde{\nu}$ = 2962, 1611, 1574, 1562, 1412, 1371, 1263, 1168, 1132, 1106, 877, 840, 772, 687 cm^{-1}.

2-Butyl-6-phenyl-4-(trifluoromethyl)pyridine (5c): Starting from 3-hydroxy-1-phenyl-3-(trifluoromethyl)non-4-yn-1-one (298 mg, 1 mmol) (**3c**) and urea (72 mg, 1.2 mmol); **5c** was isolated as a light-orange liquid; yield: 145 mg (52%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.90 (t, 3H, CH_3, ^3J = 7.2 Hz), 1.39 (m, 2H, CH_2), 1.73 (m, 2H, CH_2), 2.86 (t, 2H, CH_2, ^3J = 7.8 Hz), 7.18 (d, 1H, H-4‘, ^3J = 8.4 Hz), 7.39 (m, 3H, H-3, H-3′, H-5′), 7.65 (s, 1H, H-5), 7.95 (m, 2H, H-2′, H-6′); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 13.9 (CH_3), 22.5 (CH_2), 31.7 (CH_2), 38.3 (CH_2), 113.2 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 116.4 (q, C-5, $^3J_{C,F}$ = 3.8 Hz), 123.2 (q, CF_3, $^1J_{C,F}$ = 273.6 Hz), 127.1 (C-3′, C-5′), 128.8 (C-2′, C-6′), 129.5 (C-4′), 138.5 (C-1′), 139.2 (q, C-4, $^2J_{C,F}$ = 33.3 Hz), 158.1 (C-6), 164.0 (C-2); GC-MS (EI, 70 eV): *m/z* (%) = 250 (21), 237 (100); HRMS (ESI): *m/z* = 280.1310 [M+H]$^+$, calcd. for $C_{16}H_{17}F_3N$: 280.1308; IR (ATR): $\tilde{\nu}$ = 2958, 2930, 1573, 1459, 1412, 1372, 1261, 1166, 1131, 1103, 867, 773, 691, 639 cm^{-1}.

2-Octyl-6-phenyl-4-(trifluoromethyl)pyridine (5d): Starting from 3-hydroxy-1-phenyl-3-(trifluoromethyl)tridec-4-yn-1-one (354 mg, 1 mmol) (**3d**) and urea (72 mg, 1.2 mmol); **5d** was isolated as a light-orange liquid; yield: 188 mg (56%); ^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 0.79 (t, 3H, CH_3, ^3J = 6.0 Hz), 1.27 (m, 10H, CH_2), 1.72 (dd, 2H, CH_2, $^3J_1$ = 10.5 Hz, $^3J_2$ = 7.8 Hz), 2.84 (t, 2H, CH_2, ^3J = 7.8 Hz), 7.23 (s, 1H, H-3), 7.41 (m, 3H, H-3′, H-4′, H-5′), 7.68 (s, 1H, H-5), 7.98 (m, 2H, H-2′, H-6′); ^{13}C NMR (75.47 MHz, CD_2Cl_2): δ = 13.3 (CH_3), 22.2 (CH_2), 28.7 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 31.4 (CH_2), 37.9 (CH_2), 112.4 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 115.9 (q, C-5, $^3J_{C,F}$ = 3.8 Hz), 122.9 (q, CF_3, $^1J_{C,F}$ = 273.2 Hz), 126.4 (C-3′, C-5′), 128.3 (C-2′, C-6′), 129.1 (C-4′), 137.8 (C-1′), 138.5 (q, C-4, $^2J_{C,F}$ = 33.2 Hz), 157.2 (C-2), 163.6 (C-6); GC-MS (EI, 70 eV): *m/z* = (%): 264 (10), 250 (19), 237 (100); HR-MS (ESI): *m/z* = 335.1847 [M]$^+$, calcd. for $C_{20}H_{24}F_3N$: 335.1855; IR (ATR): $\tilde{\nu}$ = 2925, 1573, 1412, 1372, 1261, 1134, 879, 773, 691, 639 cm^{-1}.

2-Phenyl-6-(thiophen-2-yl)-4-(trifluoromethyl)pyridine (5e): Starting from 3-hydroxy-5-phenyl-1-(thiophen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (324 mg, 1 mmol) (**3e**) and urea (72 mg, 1.2 mmol); **5e** was isolated as light-orange crystals; yield: 220 mg (72%); mp 104–107 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.08 (dd, 1H, H-4″, $^3J_1$ = 3.6 Hz, $^3J_2$ = 1.5 Hz), 7.45 (br. m, 4H, H-3′, H-4′, H-5′, H-3″), 7.66 (m, 3H, H-2′, H-6′, H-5″), 8.06 (m, 2H, H-3, H-5); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 112.4 (q, C-5, $^3J_{C,F}$ = 3.8 Hz), 113.5 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 123.0 (q, CF_3, $^1J_{C,F}$ = 273.9 Hz), 125.7 (C-4″), 127.1 (C-3′, C-5′), 128.2 (C-3″), 128.9 (C-2′, C-4′, C-6′), 130.0 (C-5″), 137.7 (C-1′), 140.0 (q, C-4, $^2J_{C,F}$ = 33.2 Hz), 144.0 (C-1″), 153.5 (C-2), 158.1 (C-6); GC-MS (EI, 70 eV): *m/z* (%) = 305 (100) [M$^+$]; HR-MS (ESI): *m/z* = 306.0558 [M+H]$^+$, calcd. for $C_{16}H_{10}F_3NS$: 306.0559; IR (ATR): $\tilde{\nu}$ = 3068, 1568, 1436, 1403, 1373, 1337, 1264, 1167, 1126, 870, 833, 773, 714, 689, 633 cm^{-1}.

2-(4-Methoxyphenyl)-6-(thiophen-2-yl)-4-(trifluoromethyl)pyridine (5f): Starting from 3-hydroxy-5-(4-methoxyphenyl)-1-(thiophen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (354 mg, 1 mmol) (**3f**) and urea (72 mg, 1.2 mmol); **5f** was isolated as white crystals; yield: 298 mg (89%); mp 69–71 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.81 (s, 3H, OCH_3), 6.95 (m, 2H, H-2′, H-6′), 7.07 (dd, 1H, H-4″, $^3J_1$ = 2.4 Hz, $^3J_2$ = 1.2 Hz), 7.38 (dd, 1H, H-3″, $^3J_1$ = 4.2 Hz, $^4J_2$ = 0.9 Hz), 7.62 (m, 3H, H-5, H-3′, H-5′), 8.03 (m, 2H, H-3, H-5″); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 111.5 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 112.6 (q, C-5, $^3J_{C,F}$ = 3.8 Hz), 114.2 (C-2′, C-6′), 123.1 (q, CF_3, $^1J_{C,F}$ = 273.2 Hz), 125.5 (C-4″), 128.1 (C-3″), 128.4 (C-3′, C-5′), 128.7 (C-5″), 130.3 (C-4′), 139.8 (q, C-4, $^2J_{C,F}$ = 33.2 Hz), 144.2 (C-2″), 153.3 (C-2), 157.7 (C-6), 161.2 (C-1′); GC-MS (EI, 70 eV): *m/z* (%) = 335 (100) [M$^+$], 320 (12), 292 (35), 223 (11); HR-MS (ESI): *m/z* = 336.0663 [M+H]$^+$, calcd. for $C_{17}H_{13}F_3NOS$: 336.0665; IR (ATR): $\tilde{\nu}$ = 3093, 3015, 2968, 2840, 1608, 1562, 1516, 1435, 1411, 1371, 1337, 1265, 1162, 1127, 1105, 1025, 870, 831. 713, 690, 581 cm^{-1}.

2-Pentyl-6-(thiophen-2-yl)-4-(trifluoromethyl)pyridine (5g): Starting from 3-hydroxy-1-(thiophen-2-yl)-3-(trifluoromethyl)dec-4-yn-1-one (318 mg, 1 mmol) (**3g**) and urea (72 mg, 1.2 mmol); **5g** was isolated as a light-red powder; yield: 173 mg (58%); mp 47–49 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.84 (t, 3H, CH_3, ^3J = 6.9 Hz), 1.31 (m, 4H, CH_2), 1.72 (m, 2H, CH_2), 2.79 (t, 2H, CH_2, ^3J = 7.8 Hz), 7.06 (m, 2H, H-3′, H-4′), 7.33 (s, 1H, H-3), 7.56 (m, 2H, H-5, H-5′); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.5 (CH_2), 29.0 (CH_2), 31.5 (CH_2), 38.2 (CH_2), 111.4 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 116.1 (q, C-5, $^3J_{C,F}$ = 3.8 Hz), 121.8 (q, CF_3, $^1J_{C,F}$ = 273.2 Hz), 125.4 (C-4′), 128.4 (C-3′), 128.5 (C-5′), 139.6 (q, C-4, $^2J_{C,F}$ = 33.2 Hz), 144.1 (C-1′), 153.1 (C-6), 164.0 (C-2); GC-MS (EI, 70 eV): *m/z* (%) = 270 (28), 256 (42), 243 (100); HR-MS (ESI): *m/z* = 300.1025 [M+H]$^+$, calcd. for $C_{15}H_{17}F_3NS$: 300.1028; IR (ATR): $\tilde{\nu}$ = 2963, 2930, 1608, 1569, 1440, 1410, 1375, 1335, 1256, 1164, 1123, 870, 833, 794, 709, 694 cm^{-1}.

2-(Hex-5-ynyl)-6-(thiophen-2-yl)-4-(trifluoromethyl)pyridine (5h): Starting from 3-hydroxy-1-(thiophen-2-yl)-3-(trifluoromethyl)undeca-4,10-diyn-1-one (328 mg) (**3h**) and urea (72 mg, 1.2 mmol); **5h** was isolated as a yellow liquid; yield: 148 mg (48%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.59 (t, 2H, CH_2, ^3J = 6.9 Hz), 1.88 (m, 3H, CH_2, H-6‘), 2.20 (m, 2H, CH_2), 2.82 (t, 2H, CH_2, ^3J = 7.5 Hz), 7.18 (m, 2H, H-4″, H-3″), 7.35 (s, 1H, H-3), 7.56 (m, 2H, H-5, H-5″); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 18.3 (C-3′), 27.9 (C-2′), 28.1 (C-4′), 37.5 (C-1′), 68.5 (C-6′), 84.2 (C-5′), 111.6 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 116.1 (q, C-5, $^3J_{C,F}$ = 3.8 Hz), 123.0 (q, CF_3, $^1J_{C,F}$ = 273.2 Hz), 125.5 (C-4″), 128.4 (C-3″), 128.6 (C-5″), 139.2 (q, C-4, $^2J_{C,F}$ = 33.2 Hz), 144.0 (C-2″), 153.2 (C-2), 163.3 (C-6); GC-MS (EI, 70 eV): *m/z* (%) = 308 (20), 280 (19), 256 (25), 243 (100); HR-MS (ESI): *m/z* = 310.0867 [M+H]$^+$, calcd. for $C_{16}H_{15}F_3NS$: 310.0872; IR (ATR): $\tilde{\nu}$ = 3305, 2937, 2117, 1610, 1572, 1439, 1410, 1375, 1336, 1256, 1167, 1130, 873, 695, 629 cm^{-1}.

2-(Furan-2-yl)-6-(4-methoxyphenyl)-4-(trifluoromethyl)-pyridine (5i): Starting from 1-(furan-2-yl)-3-hydroxy-5-(4-methoxyphenyl)-3-(trifluoromethyl)pent-4-yn-1-one (338 mg, 1 mmol) (**3i**) and urea (72 mg, 1.2 mmol); **5i** was isolated as a yellow powder; yield: 239 mg (75%); mp 89–92 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 3.80 (s, 3H, OCH_3), 6.49 (dd, 1H, H-4″, $^3J_1$ = 1.8 Hz, $^3J_2$ = 1.8 Hz), 6.93 (m, 2H, H-3′, H-5′), 7.17 (dd, 1H, H-3″, $^3J_1$ = 1.8 Hz, $^3J_2$ = 0.6 Hz), 7.49 (dd, 1H, H-5″, $^3J_1$ = 1.8 Hz, $^3J_2$ = 0.6 Hz), 7.62 (s, 1H, H-3), 7.67 (s, 1H, H-5), 7.96 (m, 2H, H-2′, H-6′); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 55.4 (OCH_3), 110.0 (C-4″), 111.4 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 112.3 (C-3″), 112.9 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 114.2 (C-2′, C-6′), 123.1 (q, CF_3, $^1J_{C,F}$ = 273.2 Hz), 128.4 (C-3′, C-5′), 130.5 (C-4′), 139.8 (q, C-4, $^2J_{C,F}$ = 33.7 Hz), 143.9 (C-5″), 150.1 (C-2″), 153.2 (C-2), 157.9 (C-6), 161.2 (C-1′); GC-MS (EI, 70 eV): *m/z* (%) = 319 (100) [M$^+$], 276 (16), 246 (12); HR-MS (ESI): *m/z* = 319.0819, [M]$^+$, calcd. for $C_{17}H_{12}F_3NO_2$: 319.0815; IR (ATR): $\tilde{\nu}$ = 3101, 1608, 1564, 1400, 1379, 1361, 1246, 1131, 1105, 1016, 874, 837, 753, 690, 586 cm^{-1}.

2-(Furan-2-yl)-6-pentyl-4-(trifluoromethyl)pyridine (5j): Starting from 1-(furan-2-yl)-3-hydroxy-3-(trifluoromethyl)-dec-4-yn-1-one (302 mg, 1 mmol) (**3j**) and urea (72 mg, 1.2 mmol); **5j** was isolated as a red liquid; yield: 144 mg (51%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 0.94 (t, 3H, CH_3, ^3J = 1.8 Hz), 1.38 (m, 4H, CH_2), 1.78 (m, 2H, CH_2), 2.88 (t, 2H, CH_2, ^3J = 7.8 Hz), 6.55 (dd, 1H, H-4′, $^3J_1$ = 1.8 Hz, $^3J_2$ = 0.6 Hz), 7.20 (m, 2H, H-3′, H-5′), 7.25 (s, 1H, H-5), 7.70 (s, 1H, H-3); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ = 14.0 (CH_3), 22.4 (CH_2), 29.2 (CH_2), 31.5 (CH_2), 38.3 (CH_2), 110.0 (C-4′), 111.4 (d, C-5, $^3J_{C,F}$ = 3.8 Hz), 112.7 (C-3′), 116.1 (d, C-3, $^3J_{C,F}$ = 3.8 Hz), 122.9 (q, CF_3, $^1J_{C,F}$ = 273.6 Hz), 139.2 (q, C-4, $^2J_{C,F}$ = 33.7 Hz), 143.9 (C-5′), 149.8 (C-2′), 152.8 (C-2), 164.0 (C-6); GC-MS (EI, 70 eV): *m/z* (%) = 254 (11), 240 (19), 227 (100), 198 (10); HR-MS (ESI): *m/z* = 283.1175 [M]$^+$, calcd. for $C_{15}H_{16}F_3NO$: 283.1179; IR (ATR): $\tilde{\nu}$ = 2930, 2860, 1575, 1494, 1382, 1361, 1260, 1134, 1008, 884, 740, 695 cm^{-1}.

2-(Naphthalen-2-yl)-6-phenyl-4-(trifluoromethyl)pyridine (5k): Starting from 3-hydroxy-1-(naphthalen-2-yl)-5-phenyl-3-(trifluoromethyl)pent-4-yn-1-one (368 mg, 1 mmol) (**3k**) and urea (72 mg, 1.2 mmol); **5k** was isolated as a light-yellow powder; yield: 185 mg (53%); mp 97–99 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 7.44 (m, 5H, H-3′, H-4′, H-5′, H-6″, H-7″), 7.88 (br. m, 5H, H-1″, H-4″, H-5″, H-8″, H-5), 8.13 (m, 2H, H-2′, H-6′), 8.23 (dd, 1H, H-3″, $^3J_1$ = 6.9 Hz, $^3J_2$ = 1.8 Hz), 8.54 (s, 1H, H-3′); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 113.0 (q, C-3, $^3J_{C,F}$ = 3.8 Hz), 113.2 (q, C-5, $^3J_{C,F}$ = 3.8 Hz), 122.2 (q, CF_3, $^1J_{C,F}$ = 273.2 Hz), 123.4 (C-7″), 125.5 (C-5″), 125.8 (C-6″), 125.9 (C-3′, C-5′), 126.1 (C-8″), 126.7 (C-4′), 127.6 (C-2′, C-6′), 127.8 (C-1″, C-4″), 128.8 (C-3″), 132.3 (C-8a″), 133.0 (C-4a″), 134.4 (C-1′), 137.2 (C-2″), 139.0 (q, C-4, $^2J_{C,F}$ = 33.2 Hz), 157.0 (C-6), 157.3 (C-2); GC-MS (EI, 70 eV): *m/z* (%) = 349 (100) [M$^+$]; HR-MS (ESI): *m/z* = 349.1066 [M]$^+$, calcd. for $C_{22}H_{14}F_3N$: 349.1073; IR (ATR): $\tilde{\nu}$ = 2962, 1598, 1412, 1373, 1260, 1175, 1125, 1104, 1015, 796, 768, 755, 690 ,cm^{-1}.

2-(3-Fluorophenyl)-6-(naphthalen-2-yl)-4-(trifluoromethyl)pyridine (5l): Starting from 5-(3-fluorophenyl)-3-hydroxy-1-(naphthalen-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (386 mg, 1 mmol) (**3l**) and urea (72 mg, 1.2 mmol); **5l** was isolated as a light-yellow powder; yield: 242 mg (66%); mp 84–86 °C; ^{1}H NMR (300.13 MHz, CD_2Cl_2): δ = 7.13 (m, 1H, H-4′), 7.47 (m, 3H, H-2‘, H-5′, H-6′), 7.90 (m, 6H, H-1″, H-4″, H-5″, H-6″, H-7″, H-8″), 7.96 (s, 1H, H-3), 8.24 (d, 1H, H-3″, ^3J = 6.0 Hz), 8.56 (s, 1H, H-5); ^{13}C NMR (62.90 MHz, CD_2Cl_2): δ = 114.4 (d, C-2′, $^2J_{C,F}$ = 23.3 Hz), 114.5 (d, C-5, $^3J_{C,F}$ = 3.8 Hz), 115.3 (d, C-3, $^3J_{C,F}$ = 3.8 Hz),

119.0 (d, C-4′, $^2J_{C,F}$=21.4 Hz), 123.0 (d, C-5′, $^3J_{C,F}$=3.1 Hz), 123.6 (q, CF_3, $^1J_{C,F}$=273.6 Hz), 124.7 (C-6″), 127.0 (C-5″), 127.2 (C-7″), 127.5 (C-8″), 128.0 (C-6″), 129.0 (C-4″), 129.2 (C-1″), 130.8 (C-3″), 133.8 (C-8a″), 134.5 (C-4a″), 135.5 (C-2″), 140.8 (d, C-1′, $^3J_{C,F}$=4.9 Hz), 141.0 (q, C-4, $^2J_{C,F}$=34.0 Hz), 157.1 (d, C-2, $^4J_{C,F}$=1.9 Hz), 158.5 (C-6), 163.7 (d, C-3′, $^1J_{C,F}$=245.3 Hz); GC-MS (EI, 70 eV): *m/z* (%)=367 (100) [M$^+$]; HR-MS (ESI): *m/z*=367.0974 [M]$^+$, calcd. for $C_{22}H_{13}F_4N$: 367.0979; IR (ATR): $\tilde{\nu}$=3065, 1565, 1459, 1410, 1370, 1270, 1126, 861, 822, 782, 756, 694, 680 cm^{-1}.

2-(Naphthalen-2-yl)-6-pentyl-4-(trifluoromethyl)pyridine (5m): Starting from 3-hydroxy-1-(naphthalen-2-yl)-3-(trifluoromethyl)dec-4-yn-1-one (362 mg, 1 mmol) (**3m**) and urea (72 mg, 1.2 mmol); **5m** was isolated as a light-yellow liquid; yield: 173 mg (50%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=0.86 (m, 3H, CH_3), 1.36 (m, 4H, CH_2), 1.80 (m, 2H, CH_2), 2.89 (t, 2H, CH_2, ^3J=7.8 Hz), 7.24 (s, 1H, H-5′), 7.47 (m, 2H, H-1′, H-4′), 7.86 (m, 4H, H-5′, H-6′, H-7′, H-8′), 8.11 (dd, 1H, H-3′, $^3J_1$=6.9 Hz, $^3J_2$=1.8 Hz), 8.43 (s, 1H, H-3); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ=14.0 (CH_3), 25.5 (CH_2), 29.3 (CH_2), 31.6 (CH_2), 38.6 (CH_2), 113.4 (q, C-3, $^3J_{C,F}$=3.8 Hz), 116.4 (q, C-5, $^3J_{C,F}$=3.8 Hz), 123.2 (q, CF_3, $^1J_{C,F}$=273.6 Hz), 124.5 (C-5′), 126.4 (C-7′), 126.8 (C-8′, C-6′), 127.7 (C-4′), 128.6 (C-1′), 128.8 (C-3′), 133.4 (C-8a′), 133.9 (C-4a′), 135.8 (C-2′), 139.3 (q, C-4, $^2J_{C,F}$=34.0 Hz), 157.9 (C-6), 164.1 (C-2); GC-MS (EI, 70 eV): *m/z* (%)=343 (14) [M$^+$], 314 (33), 300 (50), 287 (100); HR-MS (ESI): *m/z*=343.1540 [M]$^+$, calcd. for $C_{21}H_{20}F_3N$: 343.1542; IR (ATR): $\tilde{\nu}$=3059, 2928, 2858, 1573, 1413, 1375, 1261, 1166, 1130, 857, 815, 740, 698 cm^{-1}.

6-Phenyl-4-(trifluoromethyl)-2,2′-bipyridine (5n): Starting from 3-hydroxy-5-phenyl-1-(pyridin-2-yl)-3-(trifluoro-methyl)pent-4-yn-1-one (319 mg, 1 mmol) (**3n**) or 3-hydroxy-1-phenyl-5-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (319 mg, 1 mmol) (**3q**) and urea (72 mg, 1.2 mmol); **5n** was isolated as a grey powder; yield: 255 mg (85% from **3n**); yield: 72 mg (24% from **3q**); mp 76–78 °C; ^{1}H NMR (300.13 MHz, CD_2Cl_2): δ=7.32 (m, 1H, H-5″), 7.43 (m, 3H, H-3′, H-4′, H-5′), 7.81 (m, 1H, H-3″), 7.90 (s, 1H, H-5), 8.10 (m, 2H, H-2′, H-6′), 8.58 (m, 3H, H-3, H-4″, H-6″); ^{13}C NMR (62.90 MHz, CD_2Cl_2): δ=115.3 (d, C-3, $^3J_{C,F}$=3.8 Hz), 116.0 (d, C-5, $^3J_{C,F}$=3.1 Hz), 121.7 (C-5″), 123.7 (q, CF_3, $^1J_{C,F}$=266.1 Hz), 125.0 (C-3″), 127.4 (C-3′, C-5′), 129.3 (C-2′, C-6′), 130.3 (C-4′), 137.5 (C-4″), 138.4 (C-4′), 140.4 (q, C-4, $^2J_{C,F}$=34.0 Hz), 149.6 (C-2″), 155.2 (C-2″), 157.6 (C-6), 158.1 (C-2); GC-MS (EI, 70 eV): *m/z* (%)=300 (100) [M$^+$], 231 (18); HR-MS (ESI): *m/z*=330.0866 [M]$^+$, calcd. for $C_{17}H_{11}F_3N_2$: 300.0869; IR (ATR): $\tilde{\nu}$=3060, 1585, 1567, 1405, 1370, 1263, 1120, 1059, 879, 772, 688, 661 cm^{-1}.

6-(4-Methoxyphenyl)-4-(trifluoromethyl)-2,2′-bipyridine (5o): Starting from 3-hydroxy-5-(4-methoxyphenyl)-1-(pyridin-2-yl)-3-(trifluoromethyl)pent-4-yn-1-one (349 mg, 1 mmol) (**3o**) and urea (72 mg, 1.2 mmol); **5o** was isolated as white crystals; yield: 300 mg (91%); mp 66–69 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=3.82 (s, 3H, OCH_3), 6.97 (m, 2H, H-2′, H-6′), 7.30 (m, 1H, H-5″), 7.80 (m, 2H, H-5, H-3″), 8.06 (m, 2H, H-3′, H-5′), 8.50 (s, 1H, H-3), 8.56 (d, 1H, H-6″, ^3J=9.0 Hz), 8.65 (dd, 1H, H-4″, $^3J_1$=3.0 Hz, $^3J_2$=3.0 Hz); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ=55.4 (OCH_3), 114.3 (C-2′, C-6′), 114.8 (d, C-3, C-5, $^3J_{C,F}$=3.8 Hz), 121.4 (C-3″), 123.2 (q, CF_3, $^1J_{C,F}$=273.6 Hz), 124.4 (C-5″), 128.4 (C-3′, C-5′), 130.7 (C-4′), 137.0 (C-4″), 140.1 (q, C-4, $^2J_{C,F}$=34.0 Hz), 149.2 (C-2″), 155.0 (C-6), 156.9 (C-2), 161.2 (C-1′). GC-MS (EI, 70 eV): *m/z* (%)=330 (100) [M$^+$], 315 (12), 287 (12); HR-MS (ESI): *m/z*=330.0975 [M]$^+$, calcd. for $C_{18}H_{13}F_3N_2O$: 330.0975; IR (ATR): $\tilde{\nu}$=2962, 1607, 1585, 1562, 1515, 1408, 1372, 1262, 1245, 1121, 1029, 837, 793, 660 cm^{-1}.

6-(Cyclohexylmethyl)-4-(trifluoromethyl)-2,2′-bipyridine (5p): Starting from 6-cyclohexyl-3-hydroxy-1-(pyridin-2-yl)-3-(trifluoromethyl)hex-4-yn-1-one (339 mg, 1 mmol) (**3p**) and urea (72 mg, 1.2 mmol); **5p** was isolated as a greenish liquid; yield: 224 mg (70%); ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=1.15 (m, 5H, Cy), 1.79 (m, 6H, Cy), 2.74 (d, 2H, CH_2, ^3J=6.0 Hz), 7.24 (s, 1H, H-5), 7.27 (m, 1H, H-5′), 7.77 (m, 1H, H-3′), 8.42 (m, 2H, H-3, H-6′), 8.63 (m, 1H, H-4′); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ=26.2 (CH_2), 26.4 (CH_2), 33.1 (CH_2), 38.4 (CH), 46.2 (CH_2), 114.0 (d, C-3, $^3J_{C,F}$=3.1 Hz), 118.8 (d, C-5, $^3J_{C,F}$=3.1 Hz), 121.4 (C-5′), 123.2 (q, CF_3, $^1J_{C,F}$=270.9 Hz), 124.2 (C-3′), 137.0 (C-4′), 139.2 (q, C-4, $^2J_{C,F}$=34.0 Hz), 149.2 (C-6′), 155.2 (C-2″), 156.8 (C-6), 162.3 (C-2); GC-MS (EI, 70 eV): *m/z* (%)=238 (100); HR-MS (ESI): *m/z*=321.1570 [M+H]$^+$, calcd. for $C_{18}H_{20}F_3N_2$: 321.1570; IR (ATR): $\tilde{\nu}$=2922, 2850, 1586, 1568, 1449, 1408, 1372, 1263, 1165, 1131, 793, 661 cm^{-1}.

2-(4-Methoxyphenyl)-6-(4-nitrophenyl)-4-(trifluoromethyl)pyridine (5q): Starting from 3-hydroxy-5-(4-methoxyphenyl)-1-(4-nitrophenyl)-3-(trifluoromethyl)pent-4-yn-1-one (393 mg, 1 mmol) (**3r**) and urea (72 mg, 1.2 mmol); **5q** was isolated as brown crystals; yield: 292 mg (78%); mp 136–139 °C; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ=3.83 (s, 3H, OCH_3), 6.99 (d, 2H, H-2′, H-6′, ^3J=6.0 Hz), 7.80 (s, 1H, H-3), 7.84 (s, 1H, H-5), 8.06 (d, 2H, H-3′, H-5′, ^3J=6.0 Hz), 8.28 (m, 4H, H-2″, H-3″, H-5″, H-6″); ^{13}C NMR (62.90 MHz, $CDCl_3$): δ=55.4 (OCH_3), 113.9 (q, C-5, $^3J_{C,F}$=3.1 Hz), 114.3 (C-2′, C-6′), 114.6 (q, C-3, $^3J_{C,F}$=3.1 Hz), 123.3 (q, CF_3, $^1J_{C,F}$=273.6 Hz), 124.1 (C-3″, C-5″), 127.9 (C-3′, C-5′), 128.5 (C-2″, C-6″), 130.1 (C-4′), 140.3 (q, C-4, $^2J_{C,F}$=34.0 Hz), 144.0 (C-4″), 148.6 (C-1″), 155.5 (C-2), 158.4 (C-6), 161.5 (C-1′); GC-MS (EI, 70 eV): *m/z* (%)=374 (100) [M$^+$], 328 (17), 284 (13); HR-MS (ESI): *m/z*=375.0954 [M+H]$^+$, calcd. for $C_{19}H_{14}F_3N_2O_3$:375.0951; IR (ATR): $\tilde{\nu}$=2845, 1682, 1607, 1563, 1525, 1368, 1348, 1246, 1162, 1128, 1028, 861, 827, 696 cm^{-1}.

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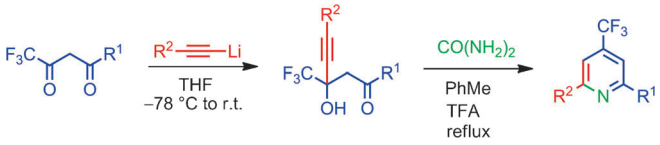
[22] CCDC 905465 contains all crystallographic details of this publication. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, U.K.; Fax: (+44)-1223-336-033 or deposit@ccdc.cam.ac.uk.

14 Synthesis of 4-Trifluoromethylpyridines by [5+1] Cyclization of 3-Hydroxy-pent-4-yn-1-ones with Urea

Adv. Synth. Catal. **2013**, *355*, 1–14



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