Palladium catalyzed synthesis of 2-trifluoromethylquinolines through a domino Sonogashira–alkyne carbocyclization process†

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A new, rapid and high-yielding method to prepare 3,4-disubstituted 2-trifluoromethylquinolines by a palladium catalyzed tandem Sonogashira–alkyne carbocyclization of β-trifluoromethyl β-enaminoketones with arynes is described. Moderate to excellent yields have been achieved under mild conditions. This reaction can also be expanded to the non-fluorine containing substrates. The reaction mechanism is also discussed.

The quinoline scaffold plays an important role as a component of antimalarial, antibacterial, antiasthmatic, antihypertensive, and antiinflammatory agents.[1–3] In particular, fluorine-containing quinolines are of significant interest because fluorine atoms sometimes play a pivotal role in bioactive compounds, and they provide a further avenue for structural elaboration.[4] For instance, the antiprotozoal drug mefloquine, which has a 2-trifluoromethylquinoline skeleton, is one of the main agents for the current treatment of malaria.[5]

Despite the importance of these heterocycles, their synthetic routes to fluorinated derivatives are limited. Classical methods include direct fluorination of a suitable functional group by nucleophilic or electrophilic fluorinating reagents,[6] direct introduction of fluoroalkyl groups by an Ullmann-type reaction of perfluoroalkyl iodides with aryl halides using copper powder,[7] and acid (or $POCl_3$) catalyzed intramolecular ring closure of the 4-anilino-1,1,1-trifluorobut-3-en-2-ones.[4e,8] Recently, transition metal catalyzed synthesis of 2-trifluoromethylquinolines was also reported.[9] All of these approaches suffer from the limited availability of the starting materials to poor yields and regioselectivity. Herein, we report a one-step and high-yielding procedure to synthesize 3,4-disubstituted 2-trifluoromethylquinolines from β-trifluoromethyl β-enaminoketones.

As listed in Table 1, 4,4,4-trifluoro-3-(2-iodophenylamino)-1-phenylbut-2-en-1one **1a** and phenylacetylene **2a** were chosen as the model substrates to screen the optimal reaction conditions. Initial experiments were performed using 1.5 equiv. of phenylacetylene **2a**, and 4 equiv. of Et_3N, in the presence of 5 mol% of $Pd(PPh_3)_2Cl_2$ and 10 mol% of CuI as the catalysts, in DMF at 60 °C under a nitrogen atmosphere overnight. The desired 2-trifluoromethylquinoline product **3a** was obtained in 12% yield (Table 1, entry 1). Interestingly, using $Pd(PPh_3)_2Cl_2$ alone also produced the target product **3a** in 12% yield (Table 1, entry 2). Encouraged by these results, different bases were examined. Both Cs_2CO_3 and K_3PO_4 (Table 1, entries 3–4) were efficient bases as compared with DMAP and pyridine (Table 1, entries 5–6). The yield was improved considerably when DBU was used as the base (Table 1, entry 7). Other palladium salts, such as $Pd(OAc)_2$ and $PdCl_2$, led to lower yields of the desired molecule (Table 1, entries 8–9), and no product was observed when CuI was used as the catalyst. Finally, other solvents such as toluene and CH_3CN were evaluated. Compared with DMF, the reaction in CH_3CN was completed in a shorter time (Table 1, entry 11), and the amount of DBU used could be reduced to 2.2 equiv. (Table 1, entry 14). Reducing the catalyst loading to 5 mol% depressed the yield and prolonged the reaction time (Table 1, entry 13). After optimization, the best reaction conditions were ascertained as 10 mol% $Pd(PPh_3)_2Cl_2$, 2.2 equiv. of DBU, and 1.5 equiv. of alkynes in MeCN at 60 °C (Table 1, entry 14). As expected, aryl iodides showed better reactivity than aryl bromides (Table 1, entry 14 *vs.* 15), and aryl chlorides showed no reactivity (Table 1, entry 16).

To investigate the scope of the proposed synthetic strategy, which includes two C–C bond-forming steps, a number of β-trifluoromethyl β-enaminoketones, which could be prepared from the condensation of simple reagents of methyl ketones with trifluoroacetimidoyl chlorides in high yields,[10] were tested.

As displayed in Table 2, when R^2 was an aromatic ring with an electron-donating group, the products were isolated in good yields (Table 2, entries 1–3). In contrast, when R^2 was an aromatic ring with an electron-withdrawing group or alkyl group, lower yields were obtained (Table 2, entries 4–6). Conversely, if R^1 was an electron-withdrawing group, the reaction was complete in a shorter time as compared with electron-donating groups (Table 2, entries 8–11). Interestingly, when 3-(5-chloro-2-iodophenylamino)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (**1m**) was used as the substrate, only 3-(5-chloro-2-(phenylethynyl)-phenylamino)-4,4,4-trifluoro-1-phenylbut-2-en-1-one **3m** was obtained, which did not undergo further cyclization even in the presence of stronger bases, such as MeONa, *t*-BuOK (Table 2, entry 12). However, substrates with R^1 as a strongly electron-withdrawing NO_2 group at the *para* position provided an intramolecular C–O bond formation product 7-nitro-2-phenyl-4-(trifluoromethyl)benzo[b][1,4]oxazepine **4n** *via* aromatic nucleophilic substitution (Table 2, entry 13), without forming the target quinoline ring. It was of interest to find that when the CF_3 group was replaced by CF_2Cl in β-fluoromethyl β-enaminoketone **1**, only the starting material was recovered. N-(2,2-difluoro-5-phenyl-furan-3(2H)-ylidene)-2-iodoaniline was obtained through a

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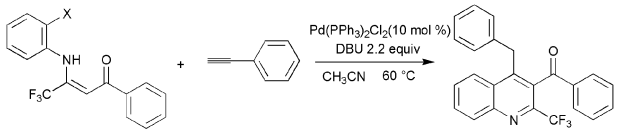
Table 1 Optimization of reaction conditions[a]

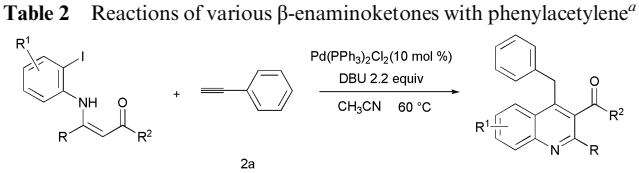


1a X = I 2a 3a

Entry	Catalyst	Base	Solvent	Time/h	Conversion (%)[b]
1	$Pd(PPh_3)_2Cl_2$(5%)/CuI(10%)	Et_3N	DMF	Overnight	12(10)
2	$Pd(PPh_3)_2Cl_2$(5%)	Et_3N	DMF	”	12(10)
3	$Pd(PPh_3)_2Cl_2$(10%)	$CsCO_3$	DMF	”	78
4	$Pd(PPh_3)_2Cl_2$(10%)	K_3PO_4	DMF	”	59
5	$Pd(PPh_3)_2Cl_2$(10%)	DMAP	DMF	”	—
6	$Pd(PPh_3)_2Cl_2$(10%)	Pyridine	DMF	”	—
7	$Pd(PPh_3)_2Cl_2$(10%)	DBU	DMF	”	99(97)
8	$Pd(OAc)_2$(10%)	DBU	DMF	”	46
9	$PdCl_2$(10%)	DBU	DMF	”	73
10	CuI (10%)	DBU	DMF	”	—
11	$Pd(PPh_3)_2Cl_2$(10%)	DBU	CH_3CN	2	99
12	$Pd(PPh_3)_2Cl_2$(10%)	DBU	Toluene	4	95
13	$Pd(PPh_3)_2Cl_2$(5%)	DBU	CH_3CN	12	92
14	$Pd(PPh_3)_2Cl_2$(10%)	DBU	CH_3CN	2	98[c,d]
15	$Pd(PPh_3)_2Cl_2$(10%)	DBU	CH_3CN	24	45[d,e]
16	$Pd(PPh_3)_2Cl_2$(10%)	DBU	CH_3CN	24	—[d,f]

[a] Reactions were carried out on a 0.2 mmol scale in DMF (2 mL) under nitrogen at 60 °C overnight with alkyne (2 equiv.) and base (4 equiv.) unless otherwise stated. [b] Reported yields were based on **1a**. Determined by ^{19}F NMR. Values in parentheses are of isolated yield. [c] Alkyne (1.5 equiv.) was used. [d] DBU (2.2 equiv.) was used. [e] X = Br. [f] X = Cl.

Table 2 Reactions of various β-enaminoketones with phenylacetylene[a]



2a

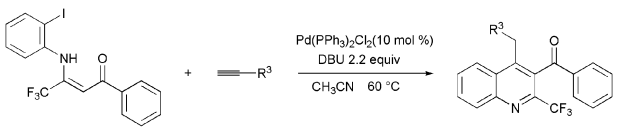
Entry	R	R_1	R_2	Product	Time/h	Yield (%)[b]
1	CF_3	H	4-$MeOC_6H_4$	**3b**	2	91
2	CF_3	H	3-$MeOC_6H_4$	**3c**	4	95
3	CF_3	H	2-Furyl	**3d**	2	91
4	CF_3	H	Cyclopropyl	**3e**	4	73
5	CF_3	H	Me	**3f**	3	77
6	CF_3	4-Me	4-ClC_6H_4	**3g**	3	86
7	CF_3	4-F	2-Naphthyl	**3h**	3	85
8	CF_3	4-Me	Ph	**3i**	4	90
9	CF_3	4-F	Ph	**3j**	2	89
10	CF_3	4-CF_3	Ph	**3k**	1	93
11	CF_3	5-MeO	Ph	**3l**	3	86
12	CF_3	5-Cl	Ph	**3m**	2	85
13	CF_3	5-NO_2	Ph	**4n**	2	75
14	Ph	H	Ph	**3o**	5 **d**	75[c]

[a] Reactions were carried out on a 0.5 mmol scale in CH_3CN (2 mL) under nitrogen at 60 °C with catalyst (10 mol%), alkyne (1.5 equiv.) and base (2.2 equiv.) unless otherwise stated. [b] Isolated yields. [c] Reaction occurred at 80 °C.

halophilic process when the CF_3 group was replaced by CF_2Br.[11] Surprisingly, when the CF_3 group of β-trifluoromethyl β-enaminoketone **1** was replaced by a phenyl group, the quinoline ring was also formed in satisfactory yield, although a longer reaction time (5 days) and higher temperature were required (Table 2, entry 14). However, when the CF_3 group of β-trifluoromethyl β-enaminoketone **1** was replaced by an alkyl group (*e.g.* methyl), no desired product could be obtained. These results indicate that the NHC(CF_3)=CHCOR structure may have a strong *ortho*-substituent chelating effect.[12–13]

The scope of the intermolecular cyclization reaction was further expanded to a variety of terminal alkynes (Table 3). Yields for all reactions were good to excellent (84–98%). Arylacetylenes bearing electron-withdrawing substituents gave higher yields and required shorter times than those bearing electron-donating substituents (Table 3, entries 1–4). All *para*-, *meta*-, and *ortho*-substituted phenylacetylenes and 2-ethynylnaphthalene were smoothly transformed into the desired products, which indicated that steric bulk did not significantly affect the reactivity (Table 3, entries 6–7). The cascade processes all occurred with good yields, even the terminal alkyne possessing a heterocyclic ring (Table 3, entries 8–9).

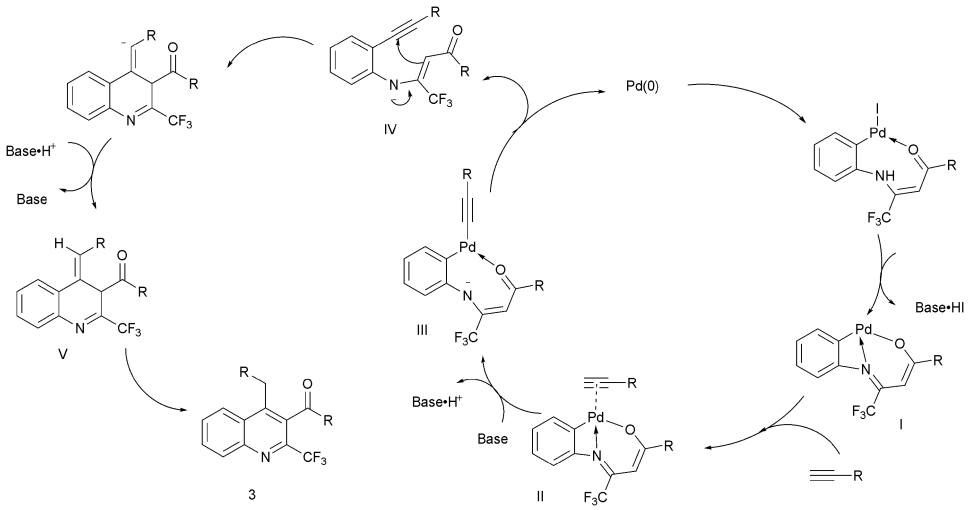
Table 3 Reactions of **1a** with representative arynes[a]



1a 2

Entry	R_3	Product	Time/h	Yield (%)[b]
1	4-Cl–C_6H_4	**3p**	1	98
2	4-OMe–C_6H_4	**3q**	2	84
3	4-F–C_6H_4	**3r**	1	96
4	4-Me–C_6H_4	**3s**	2	91
5	3-OMe–C_6H_4	**3t**	1	95
6	2-Cl–C_6H_4	**3u**	2	94
7	2-Naphthyl	**3v**	2	94
8	2-Thienyl	**3w**	1	93
9	2-Pyridyl	**3x**	1	93

[a] Reactions were carried out on a 0.5 mmol scale in CH_3CN (2 mL) under nitrogen at 60 °C with catalyst (10 mol%), alkyne (1.5 equiv.) and base (2.2 equiv.) unless otherwise stated. [b] Isolated yields.



Scheme 1 Proposed mechanism.

However, aliphatic terminal alkynes, such as 1-hexyne, did not give the desired product under the standard conditions.

A possible mechanism of this transformation is proposed in Scheme 1.[14] The first step is the oxidative addition of Pd(0) with aryl halide. The presence of an *ortho*-β-acyl-enamine group as a ligand makes this step easier (**I**). Coordination of the alkyne to the ArPdOR complex then followed. Because no copper salt is employed, and the bases are not strong enough to abstract a proton from the alkyne, a transmetalation step may be excluded. The terminal alkyne C–H bond activation is accomplished by the coordination of the alkyne to the ArPdOR complex. Upon coordination, the C–H bond is weakened, and HOR is removed from Pd(II) in the presence of a base to form an arylalkynylpalladium species **III**, which undergoes reductive elimination to afford the product **IV** regenerating the catalyst. Product **IV** then undergoes a base catalyzed alkyne carbocyclization[15] process to afford **V**, which then isomerizes to the target compound **3**.

In conclusion, we have designed a new, rapid, and high-yielding synthetic approach to 3,4-disubstituted 2-trifluoromethylquinolines *via* a tandem Sonogashira–alkyne carbocyclization process under extremely mild conditions, in which two new C–C bonds are formed during a one-pot procedure, and it works well with non-fluorine containing substrates. In addition, the NHC(CF_3)═CHCOR structure has a strong *ortho*-substituent chelating effect on the Sonogashira C–C bond formation process.

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