SCIENCE CHINA
Chemistry

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https://doi.org/10.1007/s11426-017-9160-1

Metal-free synthesis of quinolines by direct condensation of amides with alkynes: revelation of *N*-aryl nitrilium intermediates by 2D NMR techniques

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Received September 27, 2017; accepted October 25, 2017; published online December 28, 2017

Employing triflic anhydride/2-fluoropyridine as an activation system, the coupling reactions of secondary *N*-aryl amides with terminal alkynes yielded substituted quinolines in moderate to excellent yields. The reaction tolerated both electron-donating and electron-withdrawing groups at the benzamide moiety. Electron-rich aryl acetylenes served as excellent coupling partners, and aliphatic terminal alkynes such as cyclopropyl and conjugate vinyl acetylenes could also be used as reaction partners. By means of 2D NMR techniques (heteronuclear multiple bond correlation (HMBC), heteronuclear single quantum correlation (HSQC)), nitrilium ions were probed as reactive intermediates which are in contrast with that suggested by Movassaghi on the basis of *in situ* IR monitoring experiments. On the basis of these results, a plausible mechanism for the formation of quinolines was suggested.

amide activation, alkynes, quinolines, 2D NMR, nitrilium

Citation: Ye JL, Zhu YN, Geng H, Huang PQ. Metal-free synthesis of quinolines by direct condensation of amides with alkynes: revelation of *N*-aryl nitrilium intermediates by 2D NMR techniques. *Sci China Chem*, 2017, 60, https://doi.org/10.1007/s11426-017-9160-1

1 Introduction

Amide is a classical functional group. Unexpectedly, its chemistry is underdeveloped. In recent years, the direct transformation of amides has attracted considerable attention. The efforts have resulted in a host of valuable synthetic transformations of amides [1–3]. Among the methods thus developed, nucleophilic addition to amide carbonyl group occupies the central position [1]. In this regard, direct use of weakly nucleophilic alkenes and alkynes as nucleophiles is attractive for the promise of conducting chemoselective reactions [4] that are difficult when using highly reactive organometallic reagents. Very recently, we have demonstrated that by means of activation of amide carbonyl with trifluoromethanesulfonic anhydride (Tf_2O) [5], both alkenes [2j] and arenes [2k] could be used as effective nucleophiles which resulted in a highly chemoselective conversion of amides to α,β-unsaturated ketones [2j] and aromatic ketones [2k].

As a logic extension, the use of alkynes as nucleophiles was envisioned. A survey of literature showed that very few examples have been reported on the use of alkynes as nucleophiles in the reaction with amides [2b–2f,2h]. In 2006, Movassaghi *et al*. [2b] reported that by activating with Tf_2O/2-chloropyridine (2-ClPyr.), *N*-phenyl benzamides reacted with copper trimethylsilylacetylide to yield α-trimethylsilylethynyl imines (**2-I**, Scheme 1) in excellent yields. Subjection of the latter to ruthenium-catalyzed cycloisomerization produced pyridine and quinoline derivatives (**3-I**, Scheme 1). Following this two-step synthesis, an elegant single-step synthesis of pyridine derivatives employing π-nucleophiles was developed by the same group [2c,2h].

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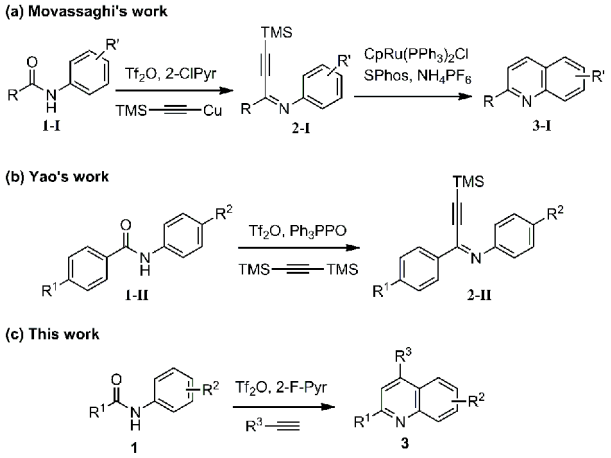


Scheme 1 Reported methods for the direct coupling of 1-trimethylsilyl-1-alkynes with *N*-aryl amides and our synthetic plan.

Among the many π-nucleophiles used, in two cases, 1-methoxy-4-(prop-1-yn-1-yl)benzene and 1-ethynyl-4-methoxybenzene, have been used as nucleophiles to yield quinolines [2c,2h]. In the same year, Yao [2d,2e] developed a concise total synthesis of the antitumor alkaloid camptothecin. Central to that synthesis is a highly efficient and mild cascade reaction of an acetylenic aniline amide triggered by bis(triphenyl)oxodiphosphonium trifluoromethanesulfonate (Hendrickson reagent) [6]. Following that discovery, the first metal-free synthesis of *N*-aryl α-alkynyl imines (**2-II**, Scheme 1) from benzanilide derivatives and 1-trimethylsilyl-1-alkynes was developed [2f]. During that study, they observed that only 1-silylated 1-alkynes are effective alkynylation agents. Moreover, in the alkynylation reactions, variable amounts of quinoline derivatives were formed as by-products. Thus, it is desirable to develop a reliable approach to quinoline derivatives by direct coupling of terminal alkynes with secondary amides. In particular, such an approach is in high demand in view of the importance of quinolines as a class of important pharmacophores [7,8]. In connection with our work on the use of Tf_2O/2-F-Pyr. [2g] as an activation system for secondary amides [2j–2l,3g], we decided to explore the direct synthesis of quinolines from secondary amides and terminal alkynes. We report herein that Tf_2O/2-F-Pyr.-promoted condensation of *N*-aryl amides with terminal alkynes allows a direct access to quinoline derivatives.

2 Experimental

2.1 Reagents and materials

Melting points were determined on a Büchi M560 Automatic Melting Point apparatus (Switzerland) and are uncorrected. Infrared spectra (IR) were measured with a Nicolet Avatar 360 FT-IR spectrometer (USA) using film pellet techniques. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500, 125 or 214 MHz, respectively. Chemical shifts (δ) are reported in ppm and respectively referenced to internal standard Me_4Si and solvent signals (Me_4Si, 0 ppm for ^{1}H NMR and $CDCl_3$, 77.0 ppm for ^{13}C NMR). Mass spectra were recorded on a Bruker Dalton ESquire 3000 plus LC-MS apparatus (ESI direct injection; Germany). HRMS spectra were recorded on a 7.0T FT-MS apparatus (Bruker, USA). Silica gel (300–400 mesh) was used for flash column chromatography, eluting with EtOAc/*n*-hexane mixture. Reactions were performed in oven-dried glassware under an argon atmosphere.

2.2 General procedure for the synthesis of quinolines

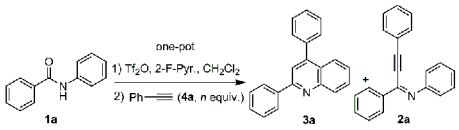
Into a dry 10-mL Schlenk tube equipped with a magnetic stirring bar were added successively a secondary amide (0.5 mmol, 1.0 equiv.), 5 mL of anhydrous 1,2-dichloroethane (DCE) and 2-fluoropyridine (2-F-Pyr.) (0.6 mmol, 1.2 equiv.) under an argon atmosphere. After being cooled to −40 °C, trifluoromethanesulfonic anhydride (Tf_2O) (155 mg, 93 μL, 0.55 mmol, 1.1 equiv.) was added dropwise via a syringe and the reaction was stirred for 5 min. Then the reaction mixture was warmed to 0 °C and maintained for 10 min. Alkynes (3.0 equiv.) in 1 mL of DCE was added dropwise at 0 °C, and the mixture was heated to 70 °C and stirred for 4 h. The reaction was quenched with a saturated $NaHCO_3$ aqueous solution (5 mL) and extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (FC) on silica gel to afford the corresponding quinoline and α-alkynyl imine.

The detailed synthesis procedures and characteristics of quinolines can be seen in the Supporting Information online.

3 Results and discussion

We opted for benzanilide (**1a**) as a substrate and the conditions that we previously established for the activation of secondary amides [2j–2l] for investigating the coupling with phenylacetylene. In the event, a solution of **1a** (1.0 equiv.) and 2-F-Pyr. (1.2 equiv.) in dichloromethane (DCM) was exposure to Tf_2O (1.1 equiv.) at −78 °C for 30 min, then phenylacetylene (**4a**, 1.1 equiv.) was added. After running at room temperature for 4 h, the desired quinoline **3a** was formed in 37% yield, along with *N*-aryl α-alkynyl imine intermediate **2a** in 5% yield. Increasing the molar equivalents of **4a** (Table 1, entries 2–5) to 3.0 resulted in an improvement of yield (**3a**: 60% yield) (entry 5). Further increase the amount of **4a** was unrewarding (entry 6). The temperature for the activation of amide can be increased

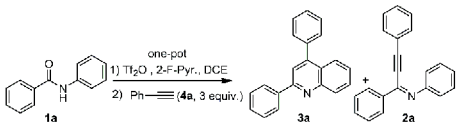
Table 1 Optimization of reaction conditions in DCM



Entry [a]	*n*	Yield (%) [b]	
		3a	**2a**
1	1.1	37	5
2	1.5	54	10
3	2.0	55	11
4	2.5	58	11
5	3.0	60	13
6	5.0	62	13
7 [c]	3.0	60	11
8 [d]	3.0	30	/
9 [e]	3.0	62	10

a) Tf_2O (1.1 equiv.), 2-F-Pyr. (1.2 equiv.), **1a** (1.0 equiv.) −78 °C, 30 min; **4a** was added and run at room temperature for 4 h; b) yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard; c) exposured to Tf_2O at −40 °C; d) exposured to Tf_2O at 0 °C; e) after addition of **4a**, the reaction was run at 40 °C.

Table 2 Optimization of the reaction conditions in DCE



Entry [a]	*T* (°C)	Time (h)	Yield (%) [b]	
			3a	**2a**
1	r.t.	4	63	16
2	70	2	52	10
3	70	4	70	10
4 [c]	70	4	74	6
5 [d]	70	4	82	5
6 [d]	70	8	83	5

a) Tf_2O (1.1 equiv.), 2-F-Pyr. (1.2 equiv.), **1a** (1.0 equiv., 0.1 M), −40 °C, 5 min; 0 °C, 10 min; then **4a** (3.0 equiv.) was added, the reaction was run at the reported temperature; b) yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard; c) the concentration of **1a** was 0.25 M; d) **4a** (3.0 equiv., 1.5 M in DCE) was added dropwise.

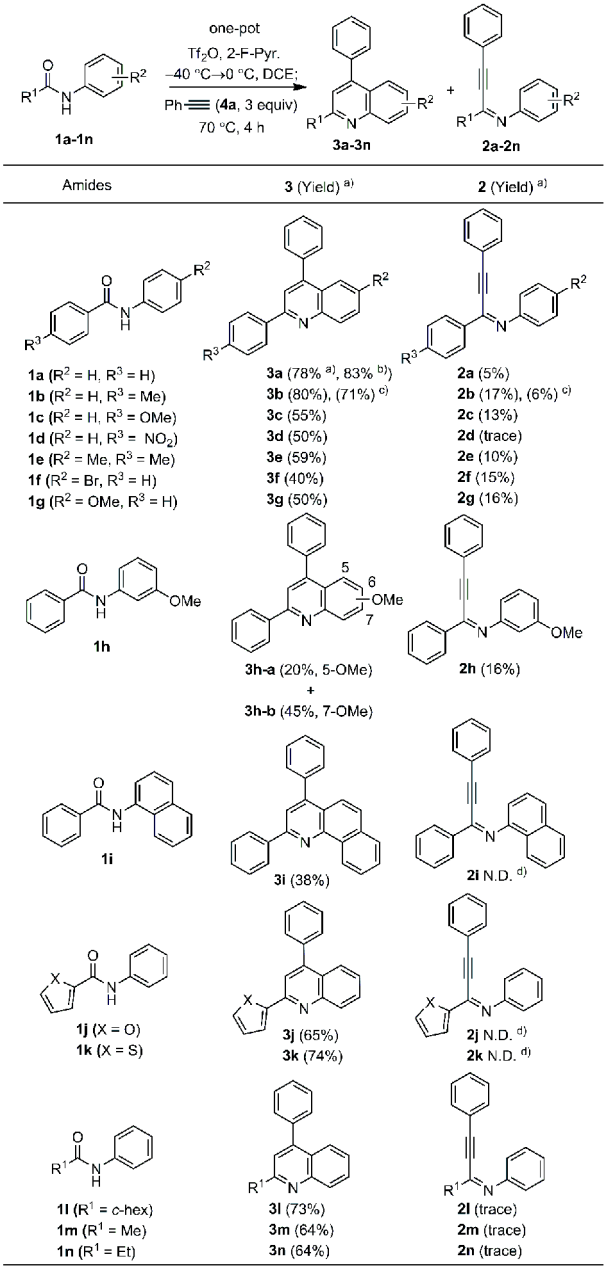
from −78 to −40 °C without affecting yield (entry 7). However, further elevating the temperature to 0 °C resulted in a drop of yield (entry 8). On the other hand, elevating reaction temperature at the second stage of the reaction (after addition of **4a**) seemed to be beneficial for the reaction (entry 9).

In the light of the latter result, DCE was employed as a solvent to replace dichloromethane (Table 2). When the reaction with **4a** was run at 70 °C for 4 h, yield of **3a** increased to 70% (entry 1), which was further improved to 74% by running the reaction at a concentration of 0.25 M (entry 4). Moreover, mode of addition of **4a** has an impact on the reaction: by dropwise addition of a solution of **4a** in DCE (1.5 M), yield of **3a** was further improved to 82% (entry 5). In addition, prolonging reaction time to 8 h was unrewarding (entry 6). Thus the optimal conditions for condensation reaction of secondary amides and alkynes were determined as treating **1a** (1.0 equiv., 0.25 M) and 2-F-Pyr. (1.2 equiv.) with Tf_2O (1.1 equiv.) in DCE at −40 °C (5 min; 0 °C, 10 min), following by addition of **4a** (3.0 equiv., 1.5 M in DCE), and stirred at 70 °C for 4 h.

After optimizing reaction conditions, the substrate scope was investigated and the results are summarized in Table 3. The reaction tolerated both electron-donating (Table 3, **1b** and **1c**) and electron-withdrawing groups (**1d**) at the benzoyl moiety. However, moderate yield was obtained from benzamides bearing a strong electron-donating (**1c**) or a strong electron-withdrawing group (**1d**). Substituents at *para*-position of the *N*-aryl moiety (**1e**–**1g**) are detrimental for the reaction: only moderate yield was obtained. The coupling of *N*-(3-methoxyphenyl)benzamide (**1h**) with phenylacetylene afforded a mixture of two regioisomers **3h-a** and **3h-b** in a combined yield of 65%. The reaction of *N*-naphthyl benzamide **1i** produced the desired product **3i** in only 38% yield and alkyne imine **2i** was not detected. The reactions of electron-rich heteroaryl carboxamides **1j** and **1k** gave corresponding quinolines **3j** and **3k** in 65% and 74% yield, respectively. Surprisingly, in both cases, alkyne imines **2j** and **2k** were not observed. In addition to aromatic amides, aliphatic amides such as **1l**, **1m** and **1n** are also suitable substrates, which reacted with phenylacetylene **4a** to afford the corresponding quinolines **3l**, **3m** and **3n** in 73%, 64%, and 64% yield, respectively. In addition, The structures of both quinoline **3m** and α-alkynyl imine **2b** were determined by single crystal X-ray diffraction analysis (Figure 1) [9].

Next, scope of alkyne was surveyed (Table 4). Arylacetylenes bearing a methoxy group at either *para*- or *ortho*-position of the aryl ring afforded the desired quinolines **3o** and **3p** in excellent yields. The alkyne bearing a *meta*-substituted methoxyl group (**4q**) also reacted smoothly to give **3q** in 74% yield. A similar yield (**3r**, 70%) was obtained from the reaction of (*p*-tolyl)acetylene (**4r**). The reaction of electron-rich heteroaryl acetylene **4t** also afforded a good yield (84%). To our good surprise, in the absence of an additional base, electron-deficient *p*-nitrophenylacetylene (**4s**) also reacted with benzanilide to give the corresponding quinoline **3s**, albeit in only 46% yield. While aliphatic alkynes bearing a cyclopropyl group and an alkenyl group (**4u** and **4v**) served well as reaction partners, low yields were obtained from the reactions of simple 1-octyne (**4w**) and that bearing an electron-withdrawing group (Cl) at α-position

Table 3 Condensation reactions of *N*-aryl *sec*-amides with phenylacetylene



a) Isolated yield; b) yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard; c) performed at 7.3 mmol (1.55 g) scale of **1b**; d) not detected.

(**4x**). Interestingly, the reaction of allene **5** at 40 °C resulted in the formation of the unexpected quinoline **3y** in 60% yield. The structure of quinoline **3y** was elucidated by single crystal X-ray diffraction analysis (Figure 2) [9]. Quinoline **3y** is a product incorporated two molecules of phenylallene **5** into benzanilide.

To demonstrate synthetic utility of the reaction, gram-scale synthesis was examined. The gram-scale reaction of **1b** with **4a** proceeded smoothly to give **3b** (1.53 g) in 71% yield along with **2b** in 6% yield (Table 3).

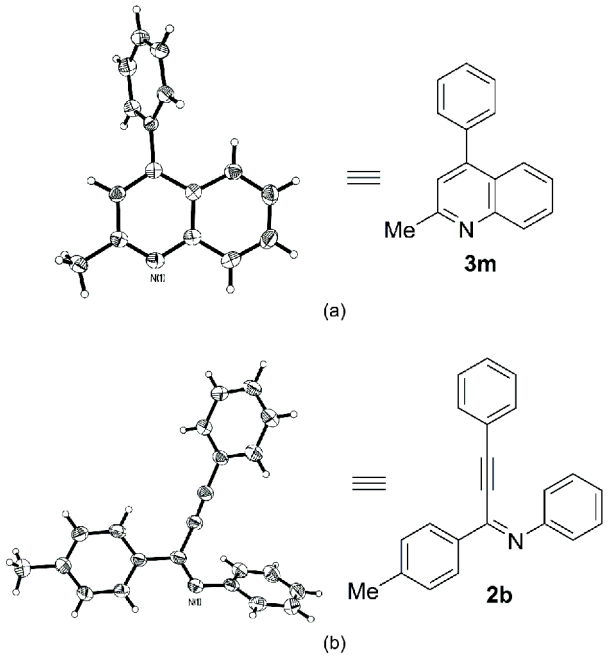


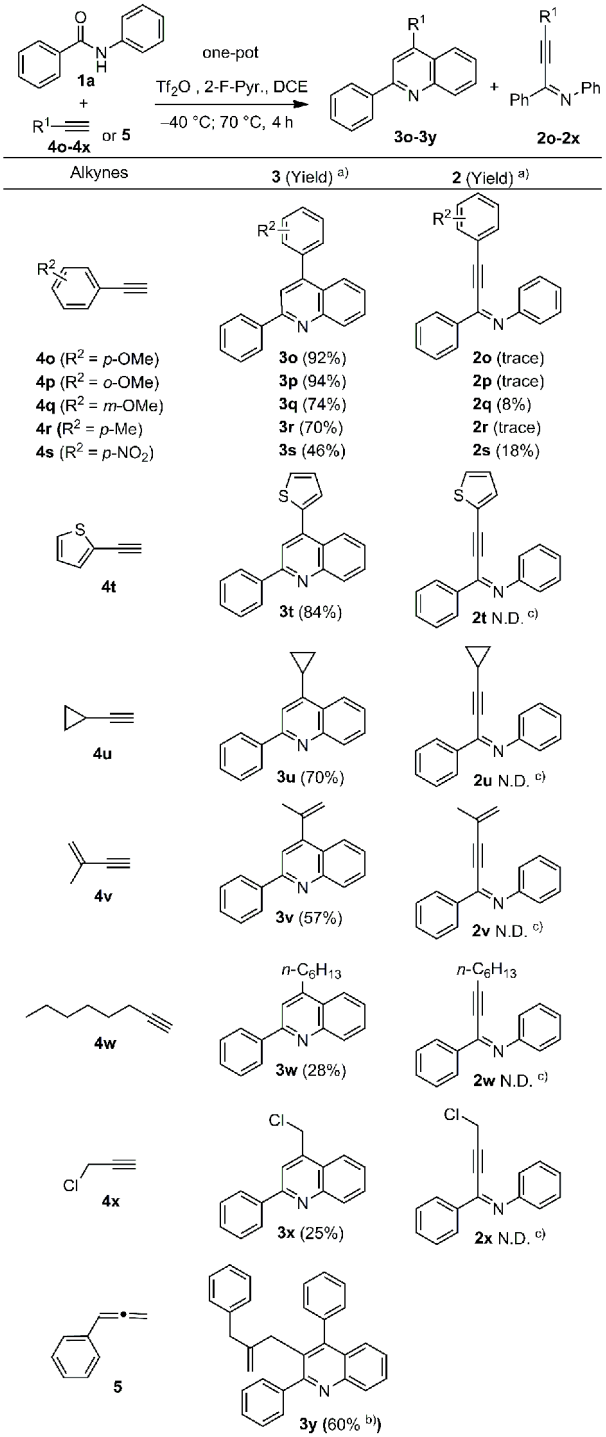
Figure 1 X-ray structures of quinoline **3m** (a) and α-alkynyl imine **2b** (b).

4 Mechanistic investigation by means of *in situ* 2D NMR techniques

In Yao's work [2f] utilizing the Hendrickson's reagent as an activator of *N*-aryl amides, the intermolecular Diels-Alder reaction between the putative imidate diene **A** (Figure 3) and an alkyne has been suggested to account for the formation of quinolines. To gain an insight into the mechanism of our Tf_2O/2-F-Pyr.-mediated condensation of secondary *N*-aryl amides with terminal alkynes, we proceeded to probe the reactive intermediates. Previously, Movassaghi and co-workers have undertaken *in situ* IR monitoring experiments to examine the intermediates generated from *N*-aryl benzamides by activation with Tf_2O in the presence of either 2-ClPyr. or 2-F-Pyr. That no detection of an IR absorption consistent with a nitrilium ion (2370 cm^{-1}) [2g] and the observation of an IR absorption at 1621 cm^{-1}, led them to suggest an amidinium ion **B** (Figure 3) [2c,2g] as the intermediate. However, in our previous *in situ* IR monitoring of the reaction between *N*-2,6-dimethylphenyl benzamides and alkenes, an absorption appeared at 2310 cm^{-1} was observed, suggesting the formation of a nitrilium ion intermediate **C** (Figure 3) [2j]. To clarify on this issue, we undertook an investigation by means of *in situ* 2D NMR techniques.

For this purpose, we selected *N*-acetyl aniline (**1m**) as a substrate, and examined the Tf_2O/acetyl aniline (**1m**) and Tf_2O/2-F-Pyr./**1m** combinations [10]. In the ^{1}H NMR spectrum of a mixture of Tf_2O and **1m**, five methyl peaks appeared at δ_H 3.27, 2.67, 2.37, 2.033 and 2.029, respectively. These methyl assignments also were confirmed by multiplicity-edited heteronuclear single quantum correlation

Table 4 Condensation reactions of benzanilide with alkynes



a) Isolated yield; b) Tf_2O (1.1 equiv.), 2-F-Pyr. (2.4 equiv.), **1a** (1.0 equiv., 0.1 M in CH_2Cl_2), −78 °C, 5 min; 0 °C, 10 min; then **5** (3.0 equiv.) was added, and the reaction was run at the 40 °C for 8 h; c) not detected.

(HSQC) experiment. The resonance at δ_H 2.67, attributable to unconsumed **1m**, indicated a 69% conversion. In the heteronuclear multiple bond correlation (HMBC) spectrum (Chart 1), the resonances at δ_H 2.37, 2.033, 2.029 correlated with δ_C 178.6, 171.1, 178.6, respectively. Because the latter are characteristic resonances of sp^2 carbon attached to N

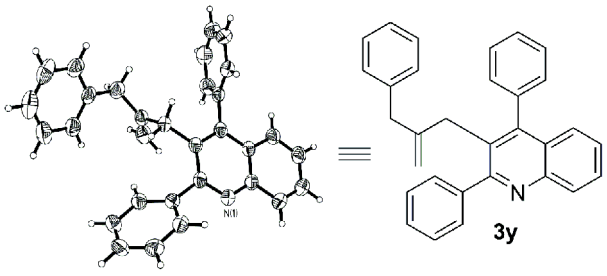


Figure 2 X-ray structure of quinoline **3y**.

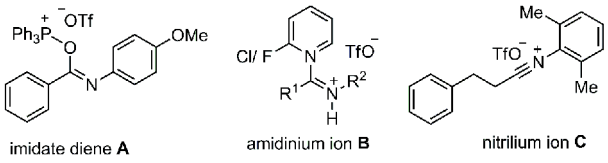


Figure 3 Structures of the activated intermediates generated from *sec*-amides previously proposed by Yao (**A**), Movassaghi (**B**), and Huang (**C**).

(Chart 1), the corresponding species were determined as **M1** (δ_H 2.033, 2.029; 40%) and **M2** (δ_H 2.37; 2%). The multi-bond correlation between residue methyl δ_H 3.27 and δ_C 116.6 (within the range of the characteristic resonance of C≡N around δ_C 115–120) explicitly indicated the formation of nitrilium ion **M3** (27%) [2j]. Notably, the unusual 4-bond correlation δ_H 3.27/δ_C 123.3 and 5-bond correlation δ_H 3.27/δ_C 128.0 also suggested a conjugated-plane structure for the nitrilium ion. It is worthy to notice that although the resonances at δ_{C2} 116.6, δ_{C4} 123.3 were readily detected through HMBC correlations, in the ^{13}C NMR, they were scarcely observable which can be ascribed to an enhanced ^{13}C-^{14}N spin-spin coupling and a quadrupolar broadening of ^{14}N in the conjugated structure.

Interestingly, in the ^{13}C NMR spectrum of a mixture of Tf_2O/2-F-Pyr./**1m**, recorded under the same conditions, only the resonances of the nitrilium **M3**, CF_3SO_3H (TfOH), and 2-F-pyridinium **M4** were observed. Thus, nitrilium ion **M3** was the predominant species in the activation system Tf_2O/2-F-Pyr./**1m** (Chart 2). This result suggested that nitrilium ion **M3** was readily formed in this activation system and 2-F-Pyr. promoted the transformation of the iminium **M1** to nitrilium **M3** [2j].

In addition, at this point the yield of nitrilium ion **M3** was only 47% as determined by ^1H NMR [11]. This may be due to the high activity of nitrilium. Indeed, the amount of nitrilium **M3** sharply decreased to 9% and more undetermined species were recorded in ^1H NMR while continued to keep the mixture in NMR tube at room temperature for 24 h.

Based on these results, the Diels-Alder-type concerted process can be ruled out because of the constrained linear geometry of nitrilium ion [2j], and a nucleophilic addition mechanism can be suggested (Scheme 2). The scenario may

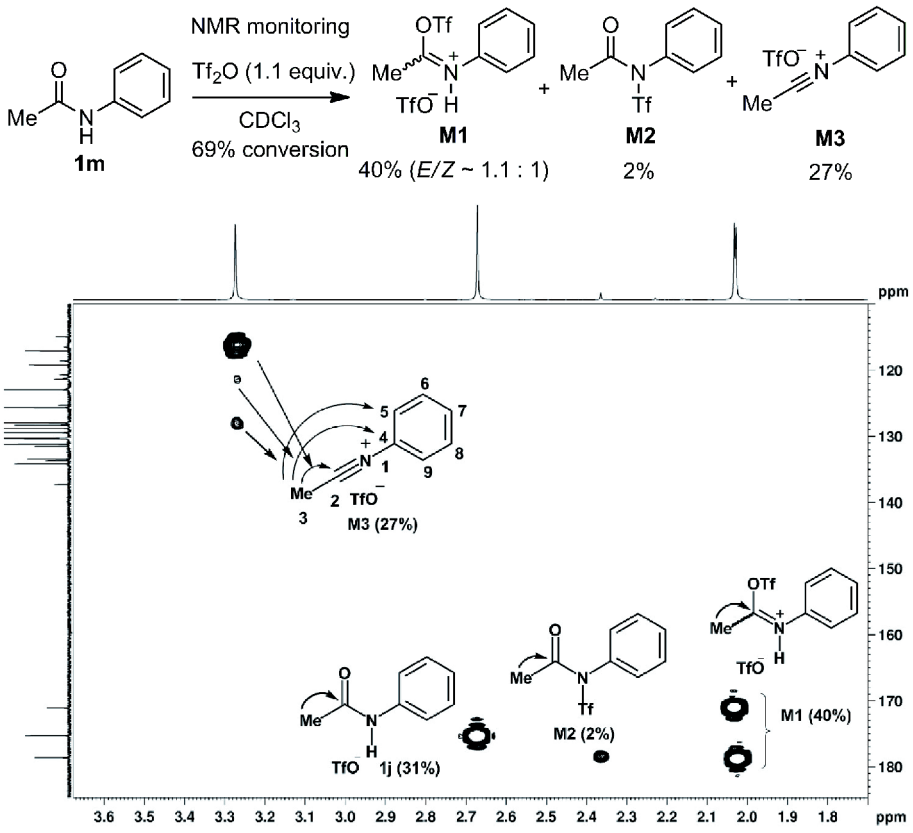


Chart 1 Regional HMBC spectrum of a mixture of **1m** (0.20 mmol) and Tf_2O (0.22 mmol) in $CDCl_3$ (1 mL).

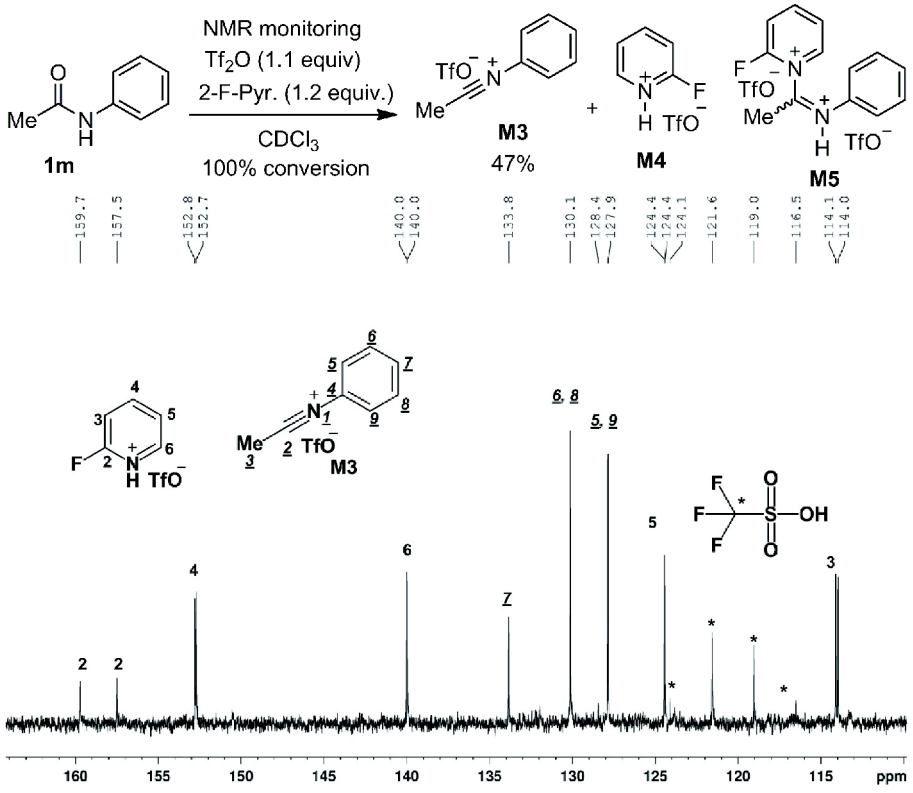
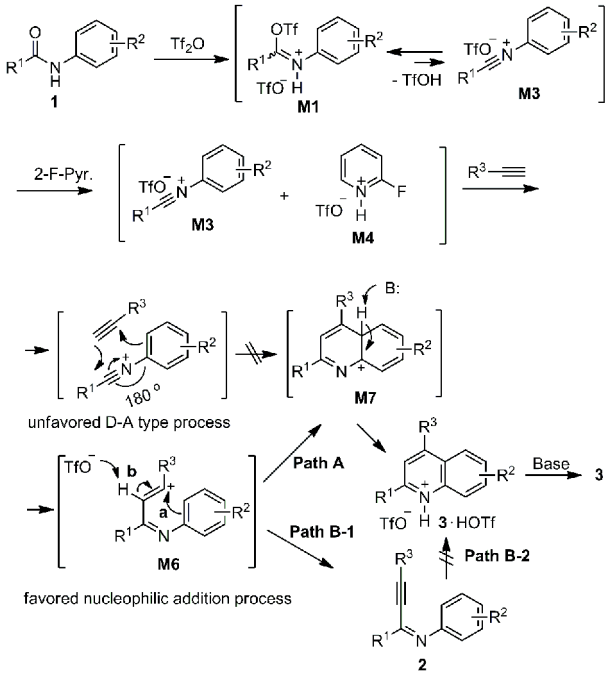
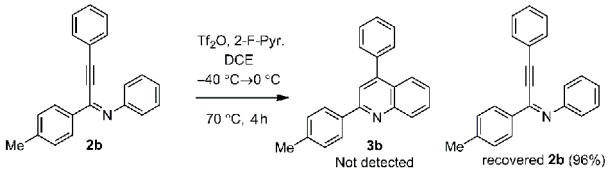


Chart 2 Regional ^{13}C NMR spectrum of a mixture of **1m** (0.20 mmol), 2-F-Pyr. (0.24 mmol) and Tf_2O (0.22 mmol) in $CDCl_3$ (1 mL).



Scheme 2 Proposed mechanism for the condensation reaction of alkynes with secondary amides.



Scheme 3 The reaction of α-alkynyl imine **2b** under standard conditions.

involve the addition of an alkyne with nitrilium ion intermediate **M3** to generate the cation intermediate **M6**, which is captured by the highly nucleophilic enamine/aryl moiety to give, via a Friedel-Crafts process, quinoline **3** as the major product (Path A). On the other hand, a base-promoted β-elimination gave the α-alkynyl imine **2** as a minor product (Path B-1). It is worth mentioning that the addition of alkynes to preformed *N*-aryl nitrilium ions similar to **M3** has been reported to give quinolines [8c].

The effects of substituents on alkynes towards the reaction can be accounted for by the proposed mechanism. Alkynes bearing a MeO group at either *para*- or *ortho*-position of a phenylacetylene (**4o** and **4p** in Table 4), being able to provide a strong resonance stabilization effect to the carbocation **M6**, afforded quinolines **3o** and **3p** in excellent yields. Thiophenyl, being a strong electron-donating and heteroaromatic group, can efficiently stabilize the carbocation group to afford **3t** in a good yield. Cyclopropyl and vinyl groups being able to stabilize α-carbocation, the corresponding alkynes **4u** and **4v** (Table 4) can be employed as nucleophiles.

To verify the proposed mechanism, the cyclization of α-alkynyl imine **2b** was attempted. Under the standard conditions, quinoline **3b** was not observed, and **2b** was recovered in 96% yield (Scheme 3). Furthermore, treating α-alkynyl imine **2b** with TfOH did not produce **3b**. These results allow suggesting that quinoline **3** can not be produced via Path B-2 (Scheme 2).

5 Conclusions

In summary, we have demonstrated that terminal alkynes could serve as effective nucleophiles in the reaction with Tf_2O/2-F-Pyr.-activated secondary *N*-aryl amides, which provided a facile access to functionalized quinolines. This method is complementary with those developed by Movassaghi and Yao that yielded *N*-aryl α-alkynyl imines as the major products. By means of 2D techniques (HMBC and HSQC), nitrilium ions were detected as reactive intermediates generated from Tf_2O/2-F-Pyr. and *sec*-amides. On the basis of this result, a plausible mechanism involving nucleophilic addition of alkynes to nitrilium ion intermediates, tandem intramolecular Friedel-Crafts-type reaction was suggested. To the best of our knowledge, this constitutes the first utilization of 2D NMR techniques to probe nitrilium ion intermediates. We believe that this would find more applications as an advantageous alternative to the *in situ* IR technique in probing reactive intermediates. In view of the versatility of amides in organic synthesis [12], our method is of synthetic value.

Acknowledgements This work was supported by the National Key R&D Program of China (2017YFA0207302), the National Natural Science Foundation of China (21332007, 21672176), the Natural Science Foundation of Fujian Province, China (2017J01021) and the Program for Changjiang Scholars and Innovative Research Team in University of Ministry of Education, China.

Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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9 The crystallographic data of compounds **3m**, **2b**, and **3y** (CCDC: 1574872, 1574871, and 1575066) can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

10 Experimental procedure: To a dry NMR tube were sequentially added amide **1m** (27 mg, 0.20 mmol), $CDCl_3$ (1 mL), Tf_2O (39 μL, 0.22 mmol), and 2-F-Pyr. (24 μL, 0.24 mmol, for Tf_2O/2-F-Pyr./**1m** combination) at −40 °C under Ar. Then the NMR tube was kept at same temperature for 5 min before allowing warm up to rt. Then NMR spectra were recorded during consecutive 5 h

11 The yield was calculated on the basis of the molar ratio of acetyl aniline (**1m**, 1.0 equiv.) and 2-F-Pyr. (1.2 equiv.). Assuming that the aryl hydrogen is 9.8 (5+4×1.2), when yield of nitrilium ion **M3** is 100%, integration of the methyl portion should have a value of 3. The observed relative integration value of 1.41 corresponds to a 47% yield

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