FULL PAPER DOI: 10.1002/adsc.202001502

Advanced Synthesis & Catalysis

Palladium-Catalyzed Carbonylative Synthesis of 2-(Trifluoromethyl)quinazolin-4(3*H*)-ones from Trifluoroacetimidoyl Chlorides and Nitro Compounds

Le-Cheng Wang,[a] Yu Zhang,[a] Zhengkai Chen,[a,*] and Xiao-Feng Wu[b, c,*]

[a] Department of Chemistry, Zhejiang Sci-Tech University, Hangzhou 310018, People's Republic of China
E-mail: zkchen@zstu.edu.cn
[b] Dalian National Laboratory for Clean Energy, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, 116023, Dalian, Liaoning, People's Republic of China
E-mail: xwu2020@dicp.ac.cn
[c] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Straße 29a, 18059 Rostock, Germany
E-mail: xiao-feng.wu@catalysis.de

Manuscript received: December 2, 2020; Revised manuscript received: January 18, 2021;
Version of record online: January 27, 2021

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202001502

Abstract: A procedure on palladium-catalyzed carbonylative reaction of trifluoroacetimidoyl chlorides and nitro compounds for the construction of pharmaceutically valuable 2-(trifluoromethyl)quinazolin-4(3*H*)-ones has been achieved. In this transformation, $Mo(CO)_6$ has been used both as a convenient CO source and a reducing reagent. This newly developed protocol is compatible with various nitro compounds and can be readily scaled up to 1 mmol scale.

Keywords: trifluoroacetimidoyl chlorides; nitro compounds; carbonylation; 2-(trifluoromethyl)quinazolin-4(*3H*)-ones; *N*-heterocyclic compounds

Introduction

Quinazolin-4(3*H*)-ones are assigned as a kind of privileged structures, which have been extensively found in various pharmaceutical molecules and natural products (Figure 1).[1] The quinazolin-4(3*H*)-one derivatives possess a series of important biological activities, such as anticancer, antiviral, antibacterial, anti-convulsant, anti-inflammatory, antifungal, and antimalarial activities.[2] Therefore, numerous elegant synthetic routes have been established for the assembly of structurally diverse quinazolin-4(3*H*)-ones in the past decades.[3] The most frequently used strategies lie in the condensation reactions of benzoic acid derivatives and also palladium-catalyzed carbonylative cyclization reactions of 2-haloanilines.[4]

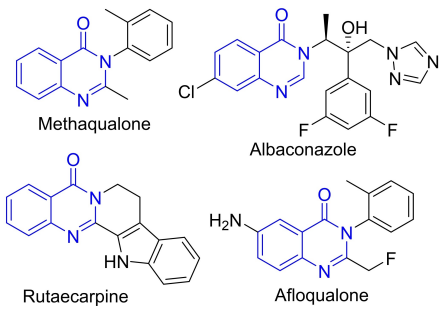
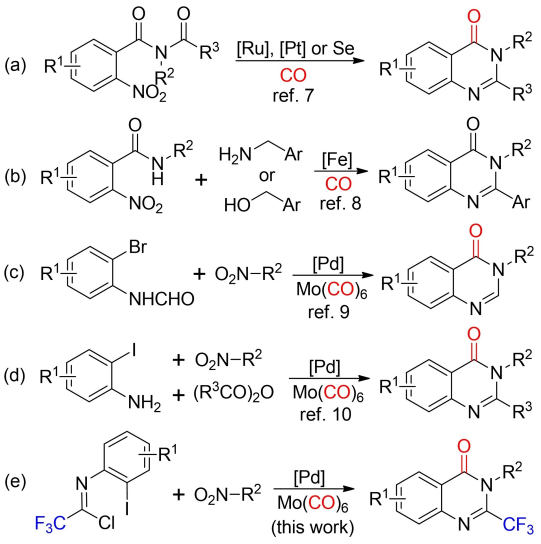


Figure 1. Selected Examples of Biologically Active Quinazolin-4(3*H*)-one Derivatives.

Palladium-catalyzed carbonylative transformations have emerged as a powerful and straightforward pathway for the synthesis of various carbonyl-containing heterocycles.[5] Among tremendous well-established carbonylative transformations, carbonylative reactions involving nitro compounds as an attractive nitrogen source attracted considerable attention due to their low cost and abundance.[6] Noteworthy is that nitroarenes are usually less expensive than the corresponding anilines. With regard to the synthesis of quinazolin-4(3*H*)-ones, several impressive methods through carbonylation by the using of nitro compounds have been developed. For instance, ruthenium-, platinum-, or even selenium-catalyzed reductive *N*-heterocyclization reactions of *N*-(2-nitrobenzoyl)amides under high-

pressure carbon monoxide produced quinazolin-4(3*H*)-ones were reported by Watanabe and Nishiyama, respectively (Scheme 1a).[7] Iron-catalyzed redox condensation reactions of 2-nitrobenzamides and benzylamines or benzylic alcohols have been disclosed for the formation of quinazolin-4(3*H*)-ones as well with CO as the reducing reagent (Scheme 1b).[8] Our group demonstrated a palladium-catalyzed carbonylative synthesis of 4(3*H*)-quinazolinones from 2-bromoformanilides, nitro compounds and $Mo(CO)_6$ (Scheme 1c).[9] Afterwards, we also described a palladium-catalyzed four-component carbonylative cyclization reaction of 2-iodoanilines, nitro compounds, acid anhydrides and $Mo(CO)_6$, which provided quinazolin-4(3*H*)-one derivatives in moderate to good yields (Scheme 1d).[10] In the above two reactions, $Mo(CO)_6$ served as both a solid CO source and a reducing reagent.[11] Although many seminal works regarding quinazolin-4(3*H*)-ones synthesis by using nitroarene as a component have been achieved, the development of more general approaches involving nitro compounds for the assembly of specifically functionalized heterocycles, such as 2-(trifluoromethyl)quinazolin-4(3*H*)-ones, is still highly desirable.

Since we consistently devote ourselves to explore efficient and practical methods for the construction of diverse trifluoromethyl-substituted *N*-heterocycles,[12] we herein report our recent discovery on palladium-catalyzed carbonylative synthesis of 2-(trifluoromethyl)quinazolin-4(3*H*)-ones from readily available trifluoroacetimidoyl chlorides[13] and nitro compounds with $Mo(CO)_6$ as a convenient CO surrogate and reductant (Scheme 1e). It is worth noting that the incorporation of trifluoromethyl group into the heterocycles can dramatically alter the physicochemical properties of the parent molecules due to the unique properties of fluorine atoms.[14]



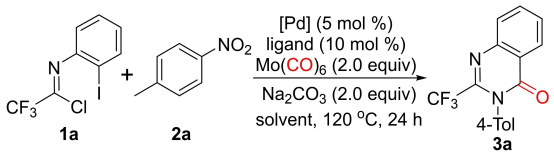
Scheme 1. Carbonylative Synthesis of Quinazolin-4(3*H*)-ones Involving Nitro Compounds.

Results and Discussion

The reaction condition was initially screened by applying 2,2,2-trifluoro-*N*-(2-iodophenyl) acetimidoyl chloride **1a** and 1-methyl-4-nitrobenzene **2a** as the model substrates, in the presence of $Pd(TFA)_2$ (5 mol%), PPh_3 (10 mol%), $Mo(CO)_6$ (2.0 equiv.) and Na_2CO_3 (2.0 equiv.) in 1,4-dioxane at 120 °C for 24 h. Gratifyingly, the desired quinazolin-4(3*H*)-one product **3a** was delivered in 78% yield (Table 1, entry 1). Stimulated by the positive result, we continued to optimize the reaction by surveying a series of palladium catalysts and $PdCl_2$ gave the best reactivity to give the product **3a** in 87% yield (Table 1, entries 2–5). Then, various phosphorus ligands, including TFP, P(*p*-CH_3-Ph)$_3$, Xantphos, dppp and dppf, were tested in the reaction, which demonstrated that the effect of dppp was superior to that of the other ligands (Table 1, entries 6–10). The examination towards solvents implied only performing the reaction in 1,4-dioxane could lead to the targeted product in excellent yield (Table 1, entries 11–14). The impact of various bases upon the transformation was remarkable, as verified that sluggish results were observed compared with that of Na_2CO_3 (Table 1, entry 15). When the loading amount of the palladium catalyst and ligand was reduced to half of its original level, the reaction yield was sharply decreased to 25% (Table 1, entry 16). Lowering the reaction temperature had a negative effect on the reaction and elevating the reaction temperature to 130 °C afforded comparable yield (Table 1, entries 17–18). To our delight, the reaction efficiency was further increased under higher concentration conditions and up to 93% isolated yield was obtained (Table 1, entry 19).

With the optimized reaction conditions in hand, we next examined the scope and limitation of this carbonylative reaction (Table 2). The reaction of diverse *N*-aryltrifluoroacetimidoyl chlorides derived from substituted 2-iodoanilines with 1-methyl-4-nitrobenzene **2a** proceeded smoothly to deliver the corresponding quinazolin-4(3*H*)-ones (**3a–k**) in good to excellent yields. The *N*-aryltrifluoroacetimidoyl chlorides bearing halogen substituents and methyl group at different position on the benzene ring were all suitable for the reaction system. The well tolerance of the halogen substituent offered the synthetic handle for the further functionalization of the obtained quinazolin-4(3*H*)-one products (**3c–e**, **3h–k**). The reaction could be readily scaled up to 1 mmol scale in 84% yield for the product **3a**. Furthermore, the good applicability of this transformation was illustrated by the viability of several

Table 1. Optimization of Reaction Conditions.[a]



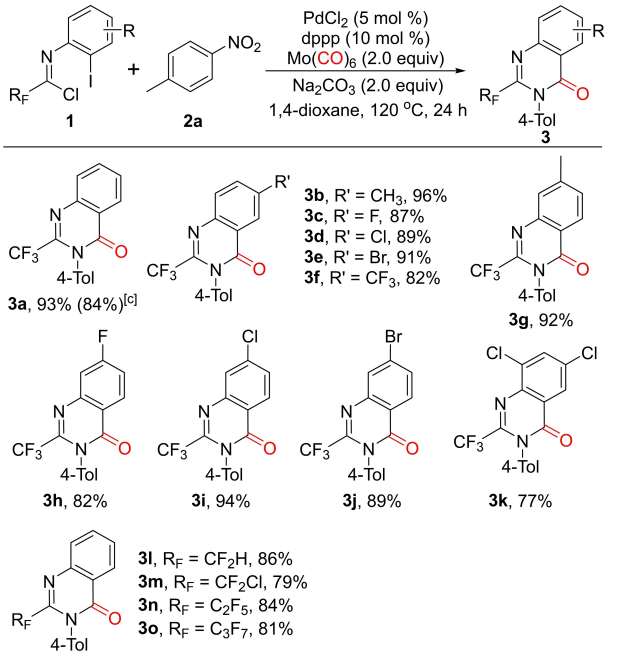
Entry	[Pd] (mol %)	Ligand (mol %)	Solvent (mL)	Yield[b] (%)
1	$Pd(TFA)_2$	PPh_3	1,4-dioxane	78
2	$Pd(OAc)_2$	PPh_3	1,4-dioxane	72
3	$PdCl_2$	PPh_3	1,4-dioxane	87
4	$Pd(acac)_2$	PPh_3	1,4-dioxane	76
5	$Pd(PPh_3)_4$	PPh_3	1,4-dioxane	86
6	$PdCl_2$	TFP	1,4-dioxane	65
7	$PdCl_2$	P(*p*-CH_3-Ph)$_3$	1,4-dioxane	82
8	$PdCl_2$	Xantphos	1,4-dioxane	81
9	$PdCl_2$	dppp	1,4-dioxane	92
10	$PdCl_2$	dppf	1,4-dioxane	91
11	$PdCl_2$	dppp	THF	40
12	$PdCl_2$	dppp	CH_3CN	36
13	$PdCl_2$	dppp	toluene	5
14	$PdCl_2$	dppp	DMF	trace
15	$PdCl_2$	dppp	1,4-dioxane	ND-35[c]
16	$PdCl_2$	dppp	1,4-dioxane	25[d]
17	$PdCl_2$	dppp	1,4-dioxane	76[e]
18	$PdCl_2$	dppp	1,4-dioxane	92[f]
19	$PdCl_2$	dppp	1,4-dioxane	98 (93)[g]

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), [Pd] (5 mol%), ligand (10 mol%), $Mo(CO)_6$ (2 equiv.), base (2.0 equiv.) in solvent (2.0 mL) at 120 °C for 24 h.
[b] Yields determined by GC analysis using dodecane as an internal standard and the isolated yields were given in parenthesis.
[c] The base was replaced with $NaHCO_3$ (19%), K_2CO_3 (25%), Cs_2CO_3 (ND), K_3PO_4 (35%), NEt_3 (27%), DIPEA (21%) or DABCO (10%), respectively.
[d] $PdCl_2$ (2.5 mol%)/dppp (5 mol%).
[e] 110 °C.
[f] 130 °C.
[g] 1,4-dioxane (1.0 mL). TFA = $-O_2CCF_3$. TFP = P(*p*-F–Ph)$_3$. DIPEA = *N*,*N*-Diisopropylethylamine. DABCO = 1,4-Diazabicyclo[2.2.2]octane. ND = No detection of the product.

other fluorinated imidoyl chlorides, which enabled the preparation of an array of different fluoroalkyl-substituted quinazolin-4(3*H*)-ones **3l–o** in 79–86% yields. It is also important to mention that we have also tried to synthesize fluorinated imidoyl chlorides from heteroaryl amines, such as pyridine moiety, but the targeted fluorinated imidoyl chlorides could not be obtained.

The generality of the protocol was further investigated by employing various nitro compounds and the results were summarized in Table 3. With respect to nitroarene substrates, the reaction was well amendable to a number of nitroarenes with

Table 2. Scope of Fluorinated Imidoyl Chlorides.[a,b]

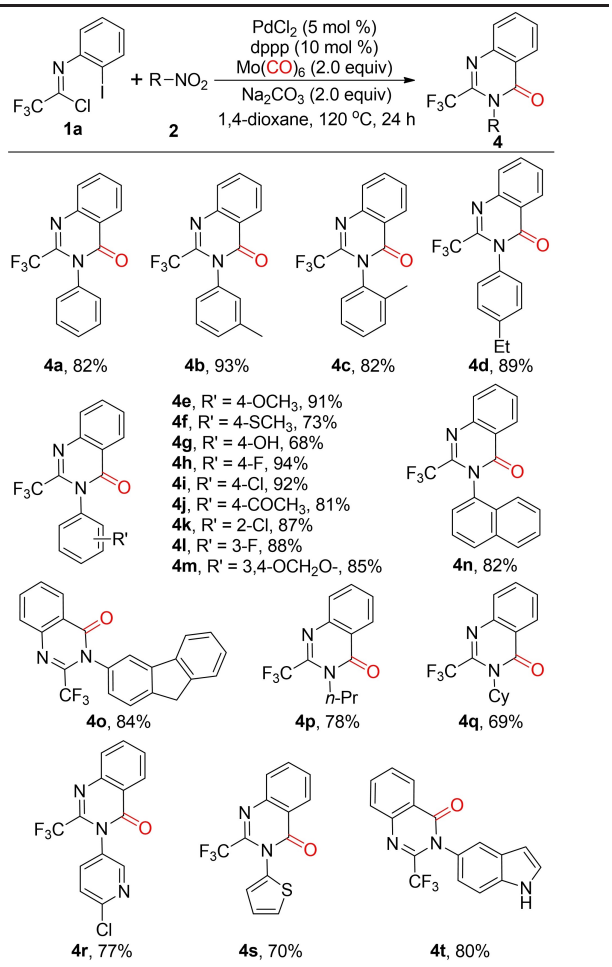


[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.24 mmol), $PdCl_2$ (5 mol%), dppp (10 mol%), $Mo(CO)_6$ (2 equiv.), Na_2CO_3 (2.0 equiv.) in 1,4-dioxane (1.0 mL) at 120 °C for 24 h.
[b] Isolated yields.
[c] 1 mmol scale.

electron-donating or -withdrawing groups, building the desired products in excellent yields at most cases (**4a–m**). The electronic effect (**4a–m**) and steric hindrance effect (**4b–c**) of the aryl ring seemingly had a little influence on the reaction outcome. It is worth mentioning that some sensitive functional groups, such as hydroxyl and acetyl (**4g** and **4j**), were all compatible with the current reaction conditions. 1-Nitronaphthalene and 2-nitro-9*H*-fluorene served as viable substrates under the standard conditions for the production of quinazolin-4(3*H*)-ones **4n–o** in good yields. Gratifyingly, the compatibility of the transformation could be further extended to aliphatic nitro compounds, as illustrated that the desired products **4p–q** with different alkyl groups were formed in 69–78% yields. Considering the great significance of heterocycles in the field of pharmaceuticals, functional materials and ligand chemistry, several heterocyclic nitro compounds were examined under the developed protocol. To our delight, the reaction was well tolerant of these heterocyclic substrates, including pyridine, thiophene and indole, providing the structurally complicated axial products **4r–t** with two different heterocyclic cores in reasonable yields.

To gain deeper understanding of the reaction mechanism, several control experiments were carried

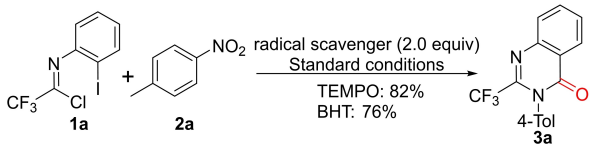
Table 3. The Scope of Nitro Compounds.[a,b]



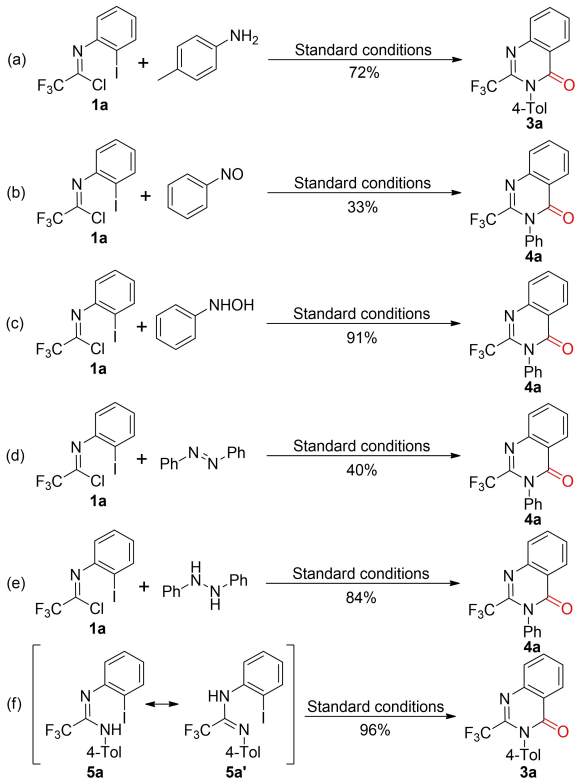
[a] Reaction conditions: **1 a** (0.20 mmol), **2** (0.24 mmol), $PdCl_2$ (5 mol%), dppp (10 mol%), $Mo(CO)_6$ (2 equiv.), Na_2CO_3 (2.0 equiv.) in 1,4-dioxane (1.0 mL) at 120 °C for 24 h.
[b] Isolated yields.

out (Scheme 2 and 3). The addition of 2.0 equiv. of TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) and BHT (2,4-di-*tert*-butyl-4-methylphenol) into the standard reaction exerted a negligible influence on the reaction outcome, which indicated that a radical pathway was possibly not involved in the transformation (Scheme 2).

Next, when 1-methyl-4-nitrobenzene **2 a** was replaced with *p*-toluidine under the standard conditions,



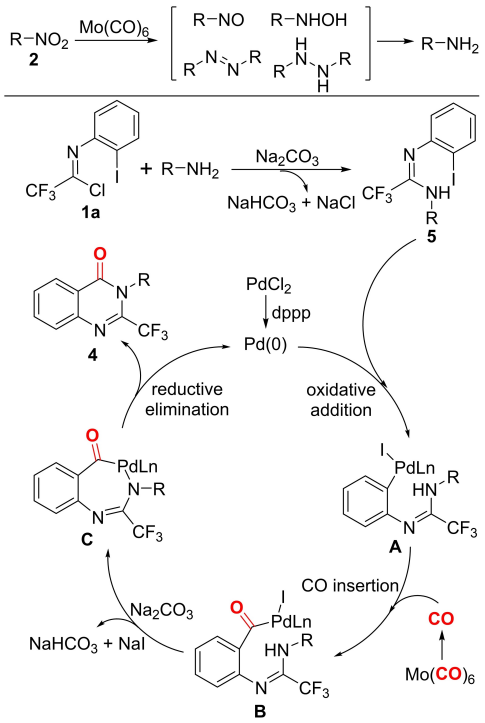
Scheme 2. Radical Trapping Experiments.



Scheme 3. Control Experiments.

the quinazolin-4(3*H*)-one product **3 a** could be obtained in 72% yield (Scheme 3a). It is speculated that the $Mo(CO)_6$ could coordinate to the aniline to some extent, thereby slightly inhibiting the reactivity of the aniline. Notably, other intermediates of nitrobenzene reduction, including nitrosobenzene (Scheme 3b), *N*-phenyl hydroxylamine (Scheme 3c), azobenzene (Scheme 3d) and 1,2-diphenylhydrazine (Scheme 3e), all reacted smoothly with trifluoroacetimidoyl chloride **1 a** under the standard conditions to give the product **4 a** in moderate to excellent yields. The observed data revealed the plausible intermediacy of the above species, which were derived from the *in-situ* reduction process of nitro compounds. We also synthesized the coupling product amidine isomers **5 a** and **5a'** from **1 a** and *p*-toluidine and subjected it into the standard conditions. As expected, the desired product **3 a** was afforded in 96% yield (Scheme 3f), which revealed that the amidine **5** possibly served as the intermediate of the reaction.

On the basis of the results from the preliminary mechanistic investigations and in precedent literatures,[10,12d] a plausible reaction mechanism was proposed (Scheme 4). First, the reduction of nitro compounds by $Mo(CO)_6$ via several possible intermediates produced amine,[9] which reacted with trifluoroacetimidoyl chloride **1 a** to give the amidine intermediate **5**. Then, the oxidative addition of Pd(0) to



Scheme 4. Plausible Reaction Mechanism.

C–I bond of **5** afforded the aryl–palladium species **A**, followed by the insertion of CO from $Mo(CO)_6$ to lead to the acyl Pd(II) complex **B**. Subsequently, the intramolecular nucleophilic cyclization of **B** in the presence of a base could generate seven-membered palladacycle intermediate **C**. Finally, the reductive elimination of **C** enabled the formation of the quinazolin-4(3*H*)-one product with the release of Pd(0) species to fulfil the catalytic cycle.

Conclusion

In summary, we have developed a general and efficient pathway for the assembly of pharmaceutically valuable 2-(trifluoromethyl)quinazolin-4(3*H*)-ones through palladium-catalyzed carbonylative reaction of trifluoroacetimidoyl chlorides and nitro compounds. Notable advantages of the methodology include readily available starting materials, a broad substrate scope, high efficiency, good applicability and easy scalability. $Mo(CO)_6$ is regarded as both a convenient CO source and a reducing reagent in this transformation, thereby no manipulating of toxic CO gas is needed.

Experimental Section

General Information

Unless otherwise noted, all reactions were carried out under N_2 atmosphere. Some reagents were from commercial sources and used as received without further purification. Column chromatography was performed on silica gel (200–300 meshes) using petroleum ether (bp. 60~90 °C) and ethyl acetate as eluent. ^{1}NMR spectra were recorded on a Bruker Avance operating at for ^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz and ^{19}F NMR at 377 MHz and spectral data were reported in ppm relative to tetramethylsilane (TMS) as internal standard and $CDCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.16), DMSO-D_6 (^{1}H NMR δ 2.50, ^{13}C NMR δ 39.52) as solvent. All coupling constants (*J*) are reported in Hz. The following abbreviations were used to describe peak splitting patterns when appropriate: s = singlet, d = doublet, dd = double doublet, ddd = double doublet of doublets, t = triplet, dt = double triplet, q = quatriplet, m = multiplet, br = broad. Gas chromatography (GC) analyses were performed on a Shimadzu GC-2014 C chromatograph equipped with a FID detector. Mass spectra (MS) were measured on spectrometer by direct inlet at 70 eV. Mass spectroscopy data of the products were collected on an HRMS-TOF instrument or Waters TOFMS GCT Premier using EI or ESI ionization. Melting points were measured with WRR digital point apparatus and not corrected.

Synthesis of Trifluoroacetimidoyl Chlorides[13b]

A 100 mL two-necked flask equipped with a septum cap, a condenser, and a Tefloncoated magnetic stir bar was charged with PPh_3 (9.84 g, 37.5 mmol), Et_3N (2.1 mL, 15 mmol), CCl_4 (20.0 mL), and TFA (1.2 mL, 15 mmol). After the solution was stirred for about 10 min (ice bath), amine (15 mmol) dissolved in CCl_4 (20.0 mL) was added. The mixture was then refluxed under stirring (12 h). After the reaction was completed, residual solid Ph_3PO, PPh_3 were washed with hexane several times. Then the hexane was filtered and concentrated under vacuum. The crude product was purified by column chromatography on silica gel or neutral alumina to afford the corresponding trifluoroacetimidoyl chloride products **1**.

General Procedure for the Synthesis of 2-(trifluoromethyl)quinazolin-4(3*H*)-ones 3/4 (Tables 2–3)

Under N_2 atmosphere, $PdCl_2$ (1.8 mg, 0.01 mmol, 5 mol%), dppp (8.2 mg, 0.02 mmol, 10 mol%), Na_2CO_3 (42.2 mg, 0.4 mmol, 2.0 equiv.), $Mo(CO)_6$ (105.6 mg, 0.4 mmol, 2.0 equiv.), **1** (0.2 mmol, 1.0 equiv.), **2** (0.24 mmol, 1.2 equiv.), 1,4-dioxane (1.0 mL) were added to an oven-dried 15 mL reaction tube. Then the tube was sealed and the mixture was stirred at 120 °C (oil bath) for 24 h. After the reaction was completed, the mixture was slowly cooled to room temperature. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (Petroleum Ether / EtOAc) to yield the product **3** or **4**.

3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3a):[12c] Yield: 93%; 56.6 mg, white solid; m.p = 140.5–141.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.6 Hz, 1H), 7.92–7.85 (m, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 145.3, 142.5 (q, $J_{(C-F)}$ = 35.2 Hz), 140.2, 135.3, 132.2,

130.1, 129.6, 128.8, 128.8, 127.5, 122.3, 118.0 (q, $J_{(C-F)}$ = 277.6 Hz), 21.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.0.

6-methyl-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 b): Yield: 96%; 61.1 mg, white solid; m.p = 112.3–113.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 2.53 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 143.3, 141.7 (q, $J_{(C-F)}$ = 35.5 Hz), 140.3, 140.2, 136.7, 132.3, 130.1, 128.9, 128.6, 127.0, 122.0, 118.1 (q, $J_{(C-F)}$ = 277.4 Hz), 21.7, 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −63.8. HRMS (ESI) calcd for $C_{17}H_{14}F_3N_2O^+$ [M + H$^+$]: 319.1053, found 319.1071.

6-fluoro-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 c): Yield: 87%; 56.1 mg, white solid; m.p = 93.3–94.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 12 Hz, 1H), 7.58 (s, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9 (d, $J_{(C-F)}$ = 252.2 Hz), 161.3, 142.0, 141.9 (q, $J_{(C-F)}$ = 38.1 Hz), 140.4, 131.9, 131.4 (d, $J_{(C-F)}$ = 8.0 Hz), 130.2, 128.7, 123.9, 123.8 (d, $J_{(C-F)}$ = 24.0 Hz) 118.0 (q, $J_{(C-F)}$ = 277.5 Hz), 112.7 (d, $J_{(C-F)}$ = 24.0 Hz), 21.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ −63.9, −108.1. HRMS (ESI) calcd for $C_{16}H_{11}F_4N_2O^+$ [M + H$^+$]: 323.0802, found 323.0822.

6-chloro-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 d): Yield: 89%; 60.2 mg, white solid; m.p = 130.1–131.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.96–7.74 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 143.9, 142.7 (q, $J_{(C-F)}$ = 35.0 Hz), 140.5, 137.8, 135.8, 131.9, 130.4, 130.2, 128.7, 127.0, 123.4, 117.9 (q, $J_{(C-F)}$ = 277.6 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.0. HRMS (ESI) calcd for $C_{16}H_{11}ClF_3N_2O^+$ [M + H$^+$]: 339.0507, found 339.0526.

6-bromo-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 e): Yield: 91%; 69.5 mg, white solid; m.p = 100.8–101.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.95 (d, J = 8.7, 1H), 7.76 (d, J = 8.7 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.17 (d, J = 7.9 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 144.2, 142.9 (q, $J_{(C-F)}$ = 35.4 Hz), 140.5, 138.6, 131.9, 130.5, 130.2, 130.2, 128.7, 123.7, 117.9 (q, $J_{(C-F)}$ = 277.6 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.0. HRMS (ESI) calcd for $C_{16}H_{11}BrF_3N_2O^+$ [M + H$^+$]: 383.0001, found 383.0020.

3-(*p*–tolyl)-2,6-bis(trifluoromethyl)quinazolin-4(3*H*)-one (3 f): Yield: 82%; 61.0 mg, white solid; m.p = 121.1–122.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.08 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.2, 147.5, 144.4 (q, $J_{(C-F)}$ = 35.7 Hz), 140.7, 131.6, 131.5 (q, $J_{(C-F)}$ = 33.6 Hz), 131.5 (q, $J_{(C-F)}$ = 3.1 Hz), 130.3, 129.9, 128.7, 125.4 (q, $J_{(C-F)}$ = 4.0 Hz), 123.4 (q, $J_{(C-F)}$ = 272.7 Hz), 122.4, 117.8 (q, $J_{(C-F)}$ = 278.0 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −62.6, −64.2. HRMS (ESI) calcd for $C_{17}H_{11}F_6N_2O^+$ [M + H$^+$]: 373.0770, found 373.0777.

7-methyl-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 g): Yield: 92%; 58.5 mg, white solid; m.p = 135.1–136.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 8.1 Hz, 1H), 7.68 (s, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 2.55 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 146.4, 145.3, 142.4 (q, $J_{(C-F)}$ = 35.1 Hz), 140.0, 132.1, 131.0, 129.9, 128.8, 128.4, 127.2, 119.7, 117.9 (q, $J_{(C-F)}$ = 277.5 Hz), 21.9, 21.3. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.0. HRMS (ESI) calcd for $C_{17}H_{14}F_3N_2O^+$ [M + H$^+$]: 319.1053, found 319.1072.

7-fluoro-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 h): Yield: 82%; 52.7 mg, white solid; m.p = 124.2–125.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36–7.33 (m, 1H), 7.54 (d, J = 9.1 Hz, 1H), 7.34 (d, J = 8.4 Hz, 3H), 7.17 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9 (d, $J_{(C-F)}$ = 256.6 Hz), 161.2, 147.3 (d, $J_{(C-F)}$ = 12.6 Hz), 143.8 (q, $J_{(C-F)}$ = 35.3 Hz), 140.4, 131.9, 130.4 (d, $J_{(C-F)}$ = 10.5 Hz), 130.2, 128.8, 119.0, 118.3 (d, $J_{(C-F)}$ = 23.4 Hz), 117.9 (q, $J_{(C-F)}$ = 277.7 Hz), 114.4 (d, $J_{(C-F)}$ = 22.3 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.1, −101.1. HRMS (ESI) calcd for $C_{16}H_{11}F_4N_2O^+$ [M + H$^+$]: 323.0802, found 323.0814.

7-chloro-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 i): Yield: 94%; 63.6 mg, white solid; m.p = 123.3–124.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.5 Hz, 1H), 7.89 (s, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 146.3, 143.7 (d, $J_{(C-F)}$ = 35.7 Hz), 141.7, 140.5, 131.9, 130.2, 129.0, 128.7, 128.4, 120.7, 117.8 (d, $J_{(C-F)}$ = 277.9 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.1. HRMS (ESI) calcd for $C_{16}H_{11}ClF_3N_2O^+$ [M + H$^+$]: 339.0507, found 339.0518.

7-bromo-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 j): Yield: 89%; 68.0 mg, white solid; m.p = 121.2–122.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.5 Hz, 1H), 8.08 (s, 1H), 7.74 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 146.3, 143.7 (q, $J_{(C-F)}$ = 35.5 Hz), 140.5, 133.0, 131.8, 131.6, 130.2, 130.1, 129.0, 128.7, 121.1, 117.8 (q, $J_{(C-F)}$ = 277.9 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.1. HRMS (ESI) calcd for $C_{16}H_{11}BrF_3N_2O^+$ [M + H$^+$]: 383.0001, found 383.0015.

6,8-dichloro-3-(*p*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (3 k): Yield: 77%; 57.3 mg, white solid; m.p = 113.5–114.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.91 (s, 1H), 7.35 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 143.1 (q, $J_{(C-F)}$ = 36.1 Hz), 141.0, 140.7, 135.7, 135.5, 134.9, 131.6, 130.3, 128.6, 125.8, 124.5, 117.8 (q, $J_{(C-F)}$ = 277.9 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.0. HRMS (ESI) calcd for $C_{16}H_{10}Cl_2F_3N_2O^+$ [M + H$^+$]: 373.0117, found 373.0127.

2-(difluoromethyl)-3-(*p*–tolyl)quinazolin-4(3*H*)-one (3 l): Yield: 86%; 49.2 mg, white solid; m.p = 126.2–127.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 7.8 Hz, 1H), 7.88–7.82 (m, 2H), 7.60 (t, J = 6.0 Hz, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.27 (t, J = 53.1 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 146.7 (t, $J_{(C-F)}$ = 24.6 Hz), 146.3, 140.3, 135.1, 131.8, 130.5, 129.0, 128.7, 128.4, 127.4, 122.2, 110.1 (t, $J_{(C-F)}$ = 245.6 Hz), 21.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ −117.2, −117.3. HRMS (ESI) calcd for $C_{16}H_{13}F_2N_2O^+$ [M + H$^+$]: 287.0660, found 287.0665.

2-(chlorodifluoromethyl)-3-(*p*–tolyl)quinazolin-4(3*H*)-one (3 m): Yield: 79%; 50.6 mg, white solid; m.p = 124.3–125.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 7.6 Hz, 1H), 7.91–7.84 (m, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H),

7.20 (d, J=8.2 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 145.6 (t, $J_{(C-F)}$=27.9 Hz), 145.3, 140.1, 135.3, 132.4, 129.9, 129.5, 129.4, 128.8, 127.6, 122.0, 120.4 (t, $J_{(C-F)}$=294.6 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −51.9. HRMS (ESI) calcd for $C_{16}H_{12}ClF_2N_2O^+$ [M+H$^+$]: 321.0601, found 321.0621.

2-(perfluoroethyl)-3-(*p*–tolyl)quinazolin-4(3*H*)-one (3 n): Yield: 84%; 59.5 mg, white solid; m.p=102.8–103.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J=7.9 Hz, 1H), 7.86 (d, J=3.6 Hz, 2H), 7.69–7.62 (m, 1H), 7.34 (d, J=8.2 Hz, 2H), 7.19 (d, J=8.2 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 145.1, 142.1 (t, $J_{(C-F)}$=26.9 Hz), 140.1, 135.2, 132.0, 130.0, 129.8, 129.0, 128.9, 127.5, 122.4, 118.4 (qt, $J_{(C-F)}$=286.4 Hz, $J_{(C-F)}$=34.3 Hz), 21.5. ^{19}F NMR (377 MHz, $CDCl_3$) δ −79.8, −107.5. HRMS (ESI) calcd for $C_{17}H_{12}F_5N_2O^+$ [M+H$^+$]: 355.0864, found 355.0883.

2-(perfluoropropyl)-3-(*p*–tolyl)quinazolin-4(3*H*)-one (3 o): Yield: 81%; 65.5 mg, white solid; m.p=89.2–90.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J=7.9 Hz, 1H), 7.89–7.84 (m, 2H), 7.653–7.67 (m, 1H), 7.34 (d, J=8.1 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.1, 145.0, 142.2 (t, $J_{(C-F)}$=26.5 Hz), 140.1, 135.2, 132.2, 132.0, 130.1, 129.8, 129.6, 128.8, 128.5, 127.5, 122.3, 118.1 (qt, $J_{(C-F)}$=288.2, $J_{(C-F)}$=33.7 Hz Hz), 112.0 (tt, $J_{(C-F)}$=248.5 Hz, $J_{(C-F)}$=28.8 Hz), 109.4, 21.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ −78.3, −104.6, 122.0. HRMS (ESI) calcd for $C_{18}H_{12}F_7N_2O^+$ [M+H$^+$]: 405.0832, found 405.0843.

3-phenyl-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 a):[12c] Yield: 82%; 47.6 mg, white solid; m.p=121.2–122.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.34 (d, J=8.5 Hz, 1H), 7.92–7.85 (m, 2H), 7.65 (t, J=8.2 Hz, 1H), 7.57–7.52 (m, 3H), 7.35–7.29 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 161.9, 145.3, 142.3 (q, $J_{(C-F)}$=35.3 Hz), 135.4, 134.9, 130.1, 129.7, 129.5, 129.2, 128.8, 127.6, 122.30, 118.0 (q, $J_{(C-F)}$=277.6 Hz). ^{19}F NMR ($CDCl_3$, 377 MHz) δ −64.0.

3-(*m*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 b):[12c] Yield: 93%; 56.6 mg, white solid; m.p=127.2–129.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J=7.0 Hz, 1H), 7.95–7.83 (m, 2H), 7.65 (t, J=8.2 Hz, 1H), 7.43 (t, J=8.1 Hz, 1H), 7.34 (d, J=7.5 Hz, 1H), 7.11 (d, J=7.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.9, 145.3, 142.4 (q, $J_{(C-F)}$=35.4 Hz), 139.5, 135.3, 134.8, 130.9, 129.6, 129.6, 129.2, 128.8, 127.5, 126.1, 122.3, 118.0 (q, $J_{(C-F)}$=277.5 Hz), 21.4. ^{19}F NMR (377 MHz, $CDCl_3$) δ −63.9.

3-(*o*–tolyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 c):[12c] Yield: 82%; 49.9 mg, white solid; m.p=122.4–124.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.36 (d, J=7.8 Hz, 1H), 7.94–7.87 (m, 2H), 7.66 (t, J=6.4 Hz, 1H), 7.45–7.35 (m, 3H), 7.21 (d, J=7.8 Hz, 1H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 161.1, 145.5, 142.5 (q, $J_{(C-F)}$=35.5 Hz), 137.0, 135.4, 134.0, 131.1, 130.4, 129.7, 129.2, 128.9, 127.6, 127.0, 122.3, 117.9 (q, $J_{(C-F)}$=277.5 Hz), 17.6. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −65.5.

3-(4-ethylphenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 d):[12c] Yield: 89%; 56.6 mg, white solid; m.p=137.8–139.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J=7.9 Hz, 1H), 7.92–7.84 (m, 2H), 7.64 (*t*, J=7.2 Hz, 1H), 7.36 (d, J=7.9 Hz, 2H), 7.21 (d, J=7.9 Hz, 2H), 2.76 (q, J=7.6 Hz, 2H), 1.31 (t, J=7.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 146.3, 145.3, 142.5 (q, $J_{(C-F)}$=35.2 Hz), 135.3, 132.3, 129.6, 128.8, 128.8, 127.5, 122.3, 118.0 (q, $J_{(C-F)}$=277.6 Hz), 28.7, 15.2. ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.0.

3-(4-methoxyphenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 e):[12c] Yield: 91%; 58.3 mg, white solid; m.p=176.8–178.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.32 (d, J=7.6 Hz, 1H), 7.91–7.83 (m, 2H), 7.63 (t, J=7.1 Hz, 1H), 7.21 (d, J=8.6 Hz, 2H), 7.03 (d, J=8.9 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 162.1, 160.6, 145.3, 142.7 (q, $J_{(C-F)}$=35.0 Hz), 135.3, 130.2, 129.6, 128.8, 127.5, 127.2, 122.3, 118.0 (q, $J_{(C-F)}$=277.5 Hz), 114.6, 55.6. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −64.1.

3-(4-(methylthio)phenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 f):[12c] Yield: 73%; 49.1 mg, white solid; m.p=172.3–173.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.36 (d, J=8.5 Hz, 1H), 8.09–7.86 (m, 2H), 7.70–7.66 (m, 1H), 7.41 (d, J=8.6 Hz, 2H), 7.24 (d, J=8.2 Hz, 2H), 2.58 (s, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 161.9, 145.3, 142.4 (q, $J_{(C-F)}$=35.2 Hz), 141.7, 135.4, 131.4, 129.7, 129.4, 128.8, 127.6, 126.6, 122.2, 118.0 (q, $J_{(C-F)}$=277.5 Hz), 15.5. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −64.1.

3-(4-hydroxyphenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 g): Yield: 68%; 41.6 mg, white solid; m.p=134.2–136.1 °C; ^{1}H NMR (400 MHz, DMSO) δ 9.90 (s, 1H), 8.19 (d, J=6.9 Hz, 1H), 7.97 (t, J=6.9 Hz, 1H), 7.89 (d, J=7.7 Hz, 1H), 7.73 (t, J=7.0 Hz, 1H), 7.28 (d, J=8.5 Hz, 2H), 6.87 (d, J=8.8 Hz, 2H). ^{13}C NMR (101 MHz, DNSO) δ 161.4, 158.3, 144.8, 142.2 (q, $J_{(C-F)}$=34.1 Hz), 135.2, 130.5, 129.5, 128.2, 126.7, 125.7, 122.2, 117.9 (q, $J_{(C-F)}$=277.4 Hz), 115.3. ^{19}F NMR (377 MHz, DMSO) δ −63.1. HRMS (ESI) calcd for $C_{15}H_{10}F_3N_2O_2^+$ [M+H$^+$]: 307.0689, found 307.0708.

3-(4-fluorophenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 h):[12c] Yield: 94%; 57.9 mg, white solid; m.p=132.6–134.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.31 (d, J=7.8 Hz, 1H), 7.92 - 7.85 (m, 2H), 7.67–7.63 (m, 1H), 7.31–7.28 (m, 2H), 7.26–7.18 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 163.3 (d, $J_{(C-F)}$=250.4 Hz), 161.9, 145.2, 142.2 (q, $J_{(C-F)}$=35.4 Hz), 135.5, 131.1 (d, $J_{(C-F)}$=9.0 Hz), 130.6, 129.8, 128.9, 127.5, 122.1, 117.9 (q, $J_{(C-F)}$=277.9 Hz), 116.6 (d, $J_{(C-F)}$=23.2 Hz). ^{19}F NMR ($CDCl_3$, 377 MHz) δ −64.0, −110.4.

3-(4-chlorophenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 i):[12c] Yield: 92%; 59.6 mg, white solid; m.p=161.3–162.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.31 (d, J=7.9 Hz, 1H), 7.92–7.86 (m, 2H), 7.67–7.63 (m, 1H), 7.55–7.50 (m, 2H), 7.25 (d, J=8.1 Hz, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 161.7, 145.2, 142.0 (q, $J_{(C-F)}$=35.4 Hz), 136.3, 135.5, 133.3, 130.6, 129.9, 129.8, 128.9, 127.5, 122.1, 117.9 (q, $J_{(C-F)}$=277.5 Hz). ^{19}F NMR ($CDCl_3$, 377 MHz) δ −63.9.

3-(4-acetylphenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4 j): Yield: 81%; 53.8 mg, white solid; m.p=131.3–132.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.4 Hz, 2H), 7.92–7.88 (m, 2H), 7.69–7.64 (m, 1H), 7.43 (d, J=8.2 Hz, 2H), 2.67 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 161.6, 145.2, 141.7 (q, $J_{(C-F)}$=

35.7 Hz), 139.0, 138.3, 135.6, 130.0, 129.7, 129.5, 129.0, 127.6, 122.1, 117.9 (q, $J_{(C-F)}$ = 277.6 Hz), 26.9. ^{19}F NMR (377 MHz, $CDCl_3$) δ −63.9. HRMS (ESI) calcd for $C_{17}H_{12}F_3N_2O_2^+$ [M + H$^+$]: 333.0845, found 333.0858.

3-(2-chlorophenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4k):[12c] Yield: 87%; 56.4 mg, white solid; m.p = 159.3–160.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.36 (d, *J* = 7.8 Hz, 1H), 7.94–7.87 (m, 2H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 160.8, 145.4, 141.9 (q, $J_{(C-F)}$ = 36.0 Hz), 135.6, 134.0, 132.9, 131.6, 131.0, 130.4, 129.8, 129.0, 127.8, 127.7, 122.2, 117.8 (q, $J_{(C-F)}$ = 277.5 Hz). ^{19}F NMR ($CDCl_3$, 377 MHz) δ −65.8.

3-(3-fluorophenyl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4l): Yield: 88%; 54.2 mg, white solid; m.p = 121.3–122.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.32 (d, *J* = 8.0 Hz, 1H), 7.92–7.87 (m, 2H), 7.68–7.65 (m, 1H), 7.55–7.49 (m, 1H), 7.30–7.24 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 162.8 (d, $J_{(C-F)}$ = 246.9 Hz), 161.6, 145.2, 141.9 (q, $J_{(C-F)}$ = 35.6 Hz), 136.1 (d, $J_{(C-F)}$ = 9.8 Hz), 135.6, 130.6 (d, $J_{(C-F)}$ = 8.8 Hz), 129.9, 128.9, 127.6, 125.2, 122.1, 117.9 (q, $J_{(C-F)}$ = 277.6 Hz), 117.5 (d, $J_{(C-F)}$ = 20.7 Hz), 117.1 (d, $J_{(C-F)}$ = 23.6 Hz). ^{19}F NMR ($CDCl_3$, 377 MHz) δ −64.0, 110.8. HRMS (ESI) calcd for $C_{15}H_9F_4N_2O^+$ [M + H$^+$]: 309.0646, found 309.0665.

3-(benzo[*d*][1,3]dioxol-5-yl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4m): Yield: 85%; 56.8 mg, white solid; m.p = 132.6–134.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.32 (d, *J* = 7.8 Hz, 1H), 7.91–7.84 (m, 2H), 7.66–7.62 (m, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.77 (d, *J* = 5.2 Hz, 2H), 6.10–6.06 (m, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 162.0, 149.0, 148.4, 145.2, 142.5 (q, $J_{(C-F)}$ = 35.2 Hz), 135.4, 129.7, 128.8, 128.0, 127.5, 122.9, 122.2, 118.0 (q, $J_{(C-F)}$ = 277.6 Hz), 110.0, 108.4, 102.3. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −63.9. HRMS (ESI) calcd for $C_{16}H_{10}F_3N_2O_3^+$ [M + H$^+$]: 335.0638, found 335.0655.

3-(naphthalen-1-yl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4n):[12c] Yield: 82%; 55.8 mg, white solid; m.p = 164.6–166.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.36 (d, *J* = 8.0 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.98–7.90 (m, 3H), 7.67 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.55–7.46 (m, 3H), 7.41 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 161.5, 145.4, 143.0 (q, $J_{(C-F)}$ = 35.4 Hz), 135.3, 134.1, 131.5, 130.7, 130.5, 129.6, 128.8, 128.6, 127.7, 127.6, 127.3, 126.7, 125.1, 122.1, 121.9, 117.8 (q, $J_{(C-F)}$ = 277.9 Hz). ^{19}F NMR ($CDCl_3$, 377 MHz) δ −64.8.

3-(9*H*-fluoren-3-yl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4o): Yield: 84%; 63.5 mg, white solid; m.p = 215.6–216.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.36 (d, *J* = 8.2 Hz, 1H), 7.93–7.87 (m, 3H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 6.6 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.48 (s, 1H), 7.42 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 3.98 (s, 2H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 162.1, 145.4, 144.3, 143.8, 143.6 (q, $J_{(C-F)}$ = 35.2 Hz), 142.4, 140.6, 135.3, 133.1, 129.7, 128.8, 127.8, 127.7, 127.6, 127.1, 125.8, 125.3, 122.3, 120.6, 120.4, 118.1 (q, $J_{(C-F)}$ = 277.7 Hz), 37.2. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −63.8. HRMS (ESI) calcd for $C_{22}H_{14}F_3N_2O^+$ [M + H$^+$]: 379.1053, found 379.1071.

3-propyl-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4p):[12d] Yield: 78%; 39.9 mg, yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.30 (d, *J* = 8.8 Hz, 1H), 7.83–7.78 (m, 2H), 7.61–7.57 (m, 1H), 4.08 (t, *J* = 8.0 Hz, 2H), 1.83–1.75 (m, 2H), 1.02 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 161.5, 145.2, 142.4 (q, $J_{(C-F)}$ = 35.5 Hz), 134.9, 129.3, 128.5, 127.1, 122.0, 118.4 (q, $J_{(C-F)}$ = 277.0 Hz), 47.0, 22.2, 11.3. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −65.8.

3-cyclohexyl-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4q):[12d] Yield: 69%; 40.9 mg; yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.26 (d, *J* = 7.8 Hz, 1H), 7.82–7.75 (m, 2H), 7.59–7.55 (m, 1H), 4.16 - 4.08 (m, 1H), 2.76 (q, *J* = 11.9 Hz, 2H), 1.93–1.91 (m, 2H), 1.78–1.68 (m, 3H), 1.41–1.30 (m, 3H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 162.1, 144.7, 142.7 (q, $J_{(C-F)}$ = 34.3 Hz), 134.7, 129.2, 128.3, 126.9, 123.3, 118.7 (q, $J_{(C-F)}$ = 277.0 Hz), 61.9, 28.8, 26.5, 25.1. ^{19}F NMR ($CDCl_3$, 377 MHz) δ −64.6.

3-(6-chloropyridin-3-yl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4r): Yield: 77%; 50.1 mg, white solid; m.p = 107.6–108.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 8.36 (s, 1H), 8.30 (d, *J* = 7.9 Hz, 1H), 7.93–7.89 (m, 2H), 7.71–7.62 (m, 2H), 7.53 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz) δ (ppm) 161.5, 153.0, 149.7, 145.0, 141.3 (q, $J_{(C-F)}$ = 35.9 Hz), 139.6, 135.9, 130.9, 130.2, 129.1, 127.6, 125.1, 121.8, 117.8 (q, $J_{(C-F)}$ = 277.4 Hz). ^{19}F NMR ($CDCl_3$, 377 MHz) δ −64.0. HRMS (ESI) calcd for $C_{14}H_8ClF_3N_3O^+$ [M + H$^+$]: 326.0303, found 326.0318.

3-(thiophen-2-yl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4s): Yield: 70%; 41.4 mg, white solid; m.p = 108.2–109.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 3.6 Hz, 2H), 7.68–7.64 (m, 1H), 7.53–7.47 (m, 1H), 7.13–7.07 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.0, 144.9, 142.6 (q, $J_{(C-F)}$ = 35.8 Hz), 135.7, 134.2, 130.0, 129.1, 129.0, 127.8, 127.8, 125.8, 121.8, 117.9 (q, $J_{(C-F)}$ = 277.4 Hz). ^{19}F NMR (377 MHz, $CDCl_3$) δ −64.3. HRMS (ESI) calcd for $C_{13}H_8F_3N_2OS^+$ [M + H$^+$]: 297.0304, found 297.0318.

3-(1*H*-indol-5-yl)-2-(trifluoromethyl)quinazolin-4(3*H*)-one (4t): Yield: 80%; 52.7 mg, white solid; m.p = 148.3–149.7 °C; ^{1}H NMR (DMSO, 400 MHz) δ (ppm) 11.39 (s, 1H), 8.21 (d, *J* = 7.9 Hz, 1H), 7.98 (t, *J* = 7.6 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 7.5 Hz, 1H), 7.66 (s, 1H), 7.55–7.45 (m, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.53 (s, 1H). ^{13}C NMR (DMSO, 101 MHz) δ (ppm) 161.6, 144.9, 142.4 (q, $J_{(C-F)}$ = 34.0 Hz), 135.8, 135.2, 129.5, 128.2, 127.3, 126.8, 126.8, 126.2, 122.3, 122.0, 121.0, 117.9 (q, $J_{(C-F)}$ = 277.5 Hz), 111.4, 101.7. ^{19}F NMR (DMSO, 377 MHz) δ −62.8. HRMS (ESI) calcd for $C_{17}H_{11}F_3N_3O^+$ [M + H$^+$]: 330.0849, found 330.0865.

2,2,2-trifluoro-*N*-(2-iodophenyl)-*N*-(*p*–tolyl)acetimidamide (5a): white solid; m.p = 132.8–133.7 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 9.85 (s, 1H), 7.70 (m, 2H), 7.32–6.52 (m, 6H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, DMSO-D_6) δ 149.1, 140.2 (q, $J_{(C-F)}$ = 31.7 Hz), 138.4, 135.6, 134.1, 129.1, 128.8, 124.5, 122.7, 120.5, 92.5, 20.9. ^{19}F NMR (377 MHz, DMSO-D_6) δ −62.7, −63.4, −69.6. HRMS (ESI) calcd for $C_{17}H_{11}F_3N_3O^+$ [M + H$^+$]: 405.0070, found 405.0085.

Radical Trapping Experiments (Scheme 2)

Under N_2 atmosphere, $PdCl_2$ (1.8 mg, 0.01 mmol, 5 mol%), dppp (8.2 mg, 0.02 mmol, 10 mol%), Na_2CO_3 (42.2 mg, 0.4 mmol, 2.0 equiv.), $Mo(CO)_6$ (105.6 mg, 0.4 mmol, 2.0 equiv.), **1a** (0.2 mmol, 66.6 mg, 1.0 equiv.), **2a** (32.9 mg, 0.24 mmol, 1.2 equiv.), TEMPO (62.5 mg, 0.4 mmol, 2.0 equiv.) or BHT (88.1 mg, 0.4 mmol, 2.0 equiv.), 1,4-dioxane (1.0 mL) were added to an oven-dried 15 mL reaction tube. Then the tube was sealed and the mixture was stirred at 120 °C (oil bath) for 24 h. After the reaction was completed, the mixture was slowly cooled to room temperature. After the reaction was completed, the reaction mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (Petroleum Ether / EtOAc) to yield the product **3a** as white solid in 82% (TEMPO) and 76% (BHT) yield.

Control Experiments (Scheme 3)

Under N_2 atmosphere, $PdCl_2$ (1.8 mg, 0.01 mmol, 5 mol%), dppp (8.2 mg, 0.02 mmol, 10 mol%), Na_2CO_3 (42.2 mg, 0.4 mmol, 2.0 equiv.), $Mo(CO)_6$ (105.6 mg, 0.4 mmol, 2.0 equiv.), **1a** (0.2 mmol, 66.6 mg, 1.0 equiv.), *p*-toluidine, nitrosobenzene, *N*-phenyl hydroxylamine, azobenzene or 1,2-diphenylhydrazine (0.24 mmol, 1.2 equiv.), or the single amidine **5a** (without **1a**), 1,4-dioxane (1.0 mL) were added to an oven-dried 15 mL reaction tube. Then the tube was sealed and the mixture was stirred at 120 °C (oil bath) for 24 h. After the reaction was completed, the mixture was slowly cooled to room temperature. After the reaction was completed, the reaction mixture was filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (Petroleum Ether/EtOAc) to yield the product **3a** or **4a** in 33–96% yields.

Acknowledgements

We thank the financial support from the Natural Science Foundation of Zhejiang Province (Grant No. LY19B020016).

References

[1] a) S. B. Mhaske, N. P. Argade, *Tetrahedron* **2006**, *62*, 9787–9826; b) I. Khan, S. Zaib, S. Batool, N. Abbas, Z. Ashraf, J. Iqbal, A. Saeed, *Bioorg. Med. Chem.* **2016**, *24*, 2361–2381; c) A. P. Chaudhary, A. K. Shukla, J. Pandey, P. Kant, *Chem.-Biol. Interact.* **2018**, *8*, 62–83; d) R. Bouley, D. Ding, Z. Peng, M. Bastian, E. Lastochkin, W. Song, M. A. Suckow, V. A. Schroeder, W. R. Wolter, S. Mobashery, M. Chang, *J. Med. Chem.* **2016**, *59*, 5011–5021.

[2] a) S.-L. Cao, Y.-P. Feng, Y.-Y. Jiang, S.-Y. Liu, G.-Y. Ding, R.-T. Li, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1915–1917; b) Y. Xia, Z.-Y. Yang, M.-J. Hour, S.-C. Kuo, P. Xia, K. F. Bastow, Y. Nakanishi, P. Nampoothiri, T. Hackl, E. Hamel, K.-H. Lee, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1193–1196; c) W. Anette, B. Jan, *Curr. Org. Chem.* **2003**, *7*, 659–677; d) M. T. H. Khan, R. Khan, Y. Wuxiuer, M. Arfan, M. Ahmed, I. Sylte, *Bioorg. Med. Chem.* **2010**, *18*, 4317–4327; e) I. Khan, A. Ibrar, W. Ahmed, A. Saeed, *Eur. J. Med. Chem.* **2015**, *90*, 124–169.

[3] a) U. A. Kshirsagar, *Org. Biomol. Chem.* **2015**, *13*, 9336–9352; b) R. S. Rohokale, U. A. Kshirsagar, *Synthesis* **2016**, *48*, 1253–1268; c) D. J. Connolly, D. Cusack, T. P. O'Sullivan, P. J. Guiry, *Tetrahedron* **2005**, *61*, 10153–10202; d) E. M. Beccalli, G. Broggini, G. Paladino, *J. Org. Chem.* **2004**, *69*, 5627–5630; e) J. A. Bleda, P. M. Fresneda, R. Orenes, *Eur. J. Org. Chem.* **2009**, 2490–2504; f) G. Broggini, E. Borsini, A. Fasana, *Eur. J. Org. Chem.* **2012**, 3617–3624; g) J. W. Collet, E. A. van der Nol, T. R. Roose, *J. Org. Chem.* **2020**, *85*, 7378–7385.

[4] a) Y.-P. Zhu, Z. Fei, M.-C. Liu, F.-C. Jia, A.-X. Wu, *Org. Lett.* **2013**, *15*, 378–381; b) H. Hikawa, Y. Ino, H. Suzuki, Y. Yokoyama, *J. Org. Chem.* **2012**, *77*, 7046–7051; c) C. Larksarp, H. Alper, *J. Org. Chem.* **2000**, *65*, 2773–2777; d) Z. Zheng, H. Alper, *Org. Lett.* **2008**, *10*, 829–832; e) L. He, H. Li, H. Neumann, M. Beller, X. F. Wu, *Angew. Chem. Int. Ed.* **2014**, *53*, 1420–1424; *Angew. Chem.* **2014**, *126*, 1444–1448; f) H. Yang, L.-C. Wang, W.-F. Wang, Z. Chen, X.-F. Wu, *ChemistrySelect* **2020**, *5*, 11072–11076.

[5] a) X.-F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1–35; b) J.-B. Peng, F.-P. Wu, X.-F. Wu, *Chem. Rev.* **2019**, *119*, 2090–2127; c) Z. Chen, L.-C. Wang, X.-F. Wu, *Chem. Commun.* **2020**, *56*, 6016–6030; d) R. Mancuso, N. Della Ca', L. Veltri, I. Ziccarelli, B. Gabriele, *Catalysts* **2019**, *9*, 610.

[6] a) X. Fang, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 14089–14093; *Angew. Chem.* **2013**, *125*, 14339–14343; b) F. Zhou, D.-S. Wang, X. Guan, T. G. Driver, *Angew. Chem. Int. Ed.* **2017**, *56*, 4530–4534; *Angew. Chem.* **2017**, *129*, 4601–4605; c) J.-B. Peng, H.-Q. Geng, D. Li, X. Qi, J. Ying, X.-F. Wu, *Org. Lett.* **2018**, *20*, 4988–4993; d) H.-Q. Geng, J.-B. Peng, X.-F. Wu, *Org. Lett.* **2019**, *21*, 8215–8218; e) J.-B. Peng, D. Li, H.-Q. Geng, X.-F. Wu, *Org. Lett.* **2019**, *21*, 4878–4881; f) J.-B. Peng, H.-Q. Geng, F.-P. Wu, D. Li, X.-F. Wu, *J. Catal.* **2019**, *375*, 519–523.

[7] a) M. Akazome, T. Kondo, Y. Watanabe, *J. Org. Chem.* **1993**, *58*, 310–312; b) Y. Nishiyama, M. Hirose, W. Kitagaito, N. Sonoda, *Tetrahedron Lett.* **2002**, *43*, 1855–1858.

[8] a) T. B. Nguyen, J. Le Bescont, L. Ermolenko, A. Al-Mourabit, *Org. Lett.* **2013**, *15*, 6218–6221; b) H. Wang, X. Cao, F. Xiao, S. Liu, G.-J. Deng, *Org. Lett.* **2013**, *15*, 4900–4903.

[9] L. He, M. Sharif, H. Neumann, M. Beller, X.-F. Wu, *Green Chem.* **2014**, *16*, 3763–3767.

[10] J.-B. Peng, H.-Q. Geng, W. Wang, X. Qi, J. Ying, X.-F. Wu, *J. Catal.* **2018**, *365*, 10–13.

[11] L. Åkerbladh, L. R. Odell, M. Larhed, *Synlett* **2019**, *30*, 141–155.

[12] a) S. Hu, Z. Yang, Z. Chen, X.-F. Wu, *Adv. Synth. Catal.* **2019**, *361*, 4949–4954; b) Z. Chen, W.-F. Wang, H. Yang, X.-F. Wu, *Org. Lett.* **2020**, *22*, 1980–1984; c) L.-C. Wang, S. Du, Z. Chen, X.-F. Wu, *Org. Lett.* **2020**, *22*, 5567–5571; d) Z. Chen, L.-C. Wang, J. Zhang, X.-F. Wu, *Org. Chem. Front.* **2020**, *7*, 2499–2504; e) S. Hu, H. Yang, Z. Chen, X.-F. Wu, *Tetrahedron* **2020**, *76*, 131168; f) S. Du, L.-C. Wang, Z. Yang, Z. Chen, X.-F. Wu, *Adv. Synth. Catal.* **2020**, *362*, 5130–5134.

[13] a) Z. Chen, S. Hu, X.-F. Wu, *Org. Chem. Front.* **2020**, *7*, 223–254; b) K. Tamura, H. Mizukami, K. Maeda, H. Watanabe, K. Uneyama, *J. Org. Chem.* **1993**, *58*, 32–35.

[14] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320–330; c) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432–2506; d) F. Meyer, *Chem. Commun.* **2016**, *52*, 3077–3094.

