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Efficient Synthesis of Quinazolines from Aryl Imidates and *N*-Alkoxyamide by Ir(III)-Catalyzed C–H Amidation/Cyclization

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An Ir(III) catalyst was used for the first time to realize the synthesis of quinazolines by C–H bond activation/cyclization with *N*-alkoxyamides as amidation reagents. This reaction has the advantages of wide substrate adaptability, good to excellent yields under mild conditions, short reaction times, and no need for an inert atmosphere. Importantly, several quinazolines from bioactive compounds were obtained, which highlights the importance of this new method.

Introduction

As an important pharmacophore, quinazoline and its derivatives have a wide range of pharmacological activities and always attracted a great deal of medical research interest.[1] For example, Prazosin[2] relaxes the smooth muscles of inner blood vessel walls, widens (dilates) blood vessels and lowers blood pressure. Lapatinib and Afatinib are well-known antitumor drugs.[3] Rutaecarpine,[4] one of the main active alkaloids, has long been used as a treatment for gastrointestinal diseases, headaches and as an anti-inflammatory agent (Figure 1). Therefore, organic chemists have been committed to finding new and efficient methods to synthesize quinazoline and its derivatives for many years.[5]

Recently, transition-metal-catalyzed *ortho*-C–H bond functionalization reactions that result in C–C or C–N bonds have been reported.[6] Among them, complex cyclic molecules have been efficiently synthesized via activation of *ortho*-C–H bonds and subsequent tandem reactions.[7] The strategy of using these tandem reactions to synthesize the quinazoline skeleton is worth exploring. Previous work reported that transition-metal-catalyzed tandem annulation via C–H bond activation to construct quinazoline compounds was limited to Rh and Co catalysts.[8] Previously, our group has demonstrated that *N*-alkoxyamides are a class of highly-efficient aminating reagents that connect two different bioactive compounds via C–N bonds.[9] As quinazolines are highly important in new drug discovery, it would be of interest to develop new methods for the synthesis of new quinazolines using just one bioactive compound. Herein, we report an Ir(III)-catalyzed C–H activation/amidation/annulation of imidate esters using *N*-methoxyamide as the amidating reagent. Various quinazolines were obtained in good to excellent yields under mild conditions with fifty examples synthesized. Importantly, several quinazolines from bioactive compounds were isolated and highlights the importance of this new method.

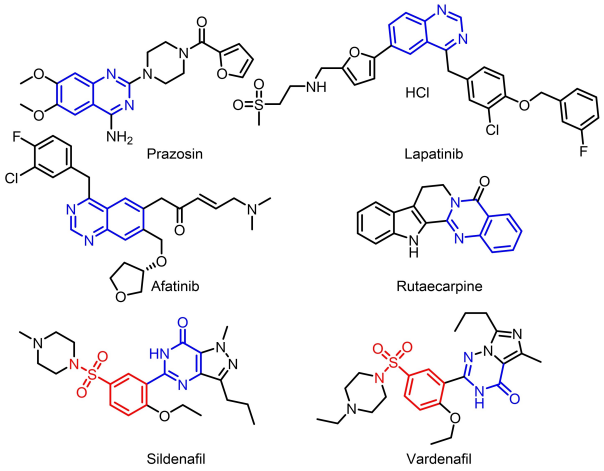

Figure 1. Selected bioactive quinazoline derivatives.

Results and Discussion

With this in mind, we initiated our investigation by reacting ethyl benzimidate **1a** with *N*-methoxyamide **2a** in the presence of $[Cp^*IrCl_2]_2$ (5 mol%) as the catalyst and $AgSbF_6$ (10 mol%) as an additive at 140 °C for 4 h (Table 1, entry 1). To our delight, the reaction afforded the expected annulated product **3aa** in 66% yield (Table 1, entry 1). Encouraged by this, different reaction temperatures were investigated. Lowering the reaction temperature to 120 °C improved the yield of **3aa** significantly

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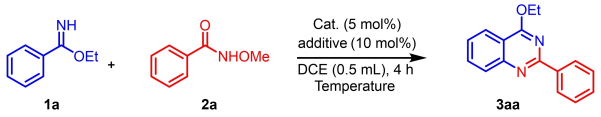
Table 1. Optimized reaction conditions.[a]



Entry[a]	Cat.	Additive	T [°C]	Yield [%][b]
1	$[Cp^*IrCl_2]_2$	$AgSbF_6$	140	66
2	$[Cp^*IrCl_2]_2$	$AgSbF_6$	120	79
3	$[Cp^*IrCl_2]_2$	$AgSbF_6$	100	70
4	$[Cp^*IrCl_2]_2$	$AgSbF_6$	80	56
5	$[Cp^*IrCl_2]_2$	AgOTf	120	67
6	$[Cp^*IrCl_2]_2$	AgTs	120	29
7	$[Cp^*IrCl_2]_2$	$AgNTf_2$	120	40
8	$[Ir(cod)Cl]_2$	$AgSbF_6$	120	trace
9	$[Cp^*RhCl_2]_2$	$AgSbF_6$	120	36
10	$[Cp^*IrCl_2]_2$	$AgSbF_6$	120	92[c]
11	–	$AgSbF_6$	120	nr
12	$[Cp^*IrCl_2]_2$	–	120	21

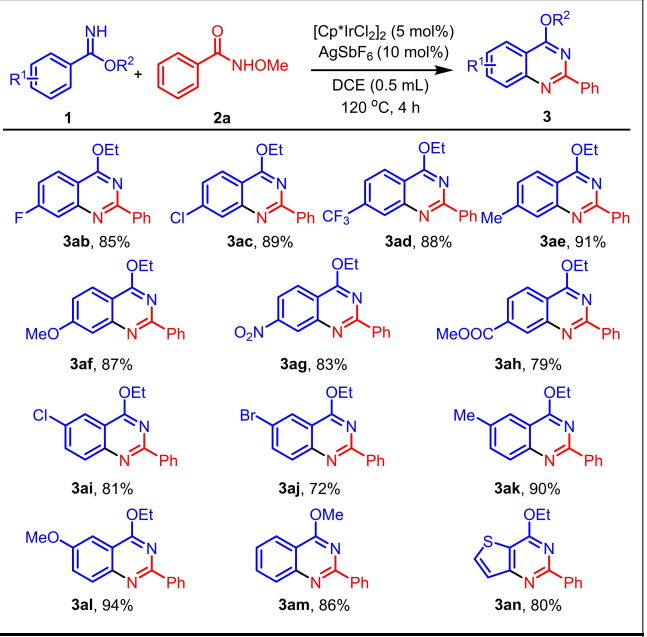
[a] Unless otherwise noted, reactions were carried out with **1a** (0.2 mmol), **2a** (0.2 mmol), **Cat.** (5 mol%) and $AgSbF_6$ (10 mol%) in DCE (0.5 mL). [b] Isolated yield. [c] **1a** (0.24 mmol), **2a** (0.2 mmol).

(to 79%, Table 1, entry 2). However, lowering reaction temperature further resulted in the incomplete conversion of raw materials, which indicated higher temperatures were necessary for this reaction (Table 1, entries 3–4). Different silver salts were tested; but none of them improved the reaction yield (Table 1, entries 5–7). Other transition-metal complexes showed lower catalytic activity (Table 1, entries 8–9). Increasing the dosage of **1a** to 0.24 mmol improved the yield of **3aa** to 92% (Table 1, entry 10). Screening of different solvents showed that DCE was the best solvent in the conversion process (Table S1). Control experiments showed that $[Cp^*IrCl_2]_2$ and $AgSbF_6$ were essential for the reaction to proceed (Table 1, entries 11–12).

After optimizing the reaction conditions, myriad substituted ethyl benzimidates **1** were tested with *N*-alkoxyamides **2a**; Table 2 summarizes those results. The substrates contained a wide variety of functional groups, including halogens, CF_3, Me, and OMe on the para position. All of them efficiently afforded the cyclization products (**3ab**–**3af**). To our surprise, strongly electron-withdrawing nitro and ester groups were also tolerated and gave the corresponding products in good yields (**3ag**–**3ah**). When the effect of the *meta*-substituents on the benzene ring was investigated, high-yield target products were obtained, and formation of the C–N bond occurred selectively on the side with less steric hindrance (**3ai**–**3al**). Changing an ethyl group to a methyl group did not impact the reactivity (**3am**). Furthermore, heterocyclic substrates containing a thiophene moiety were suitable for this system (**3an**).

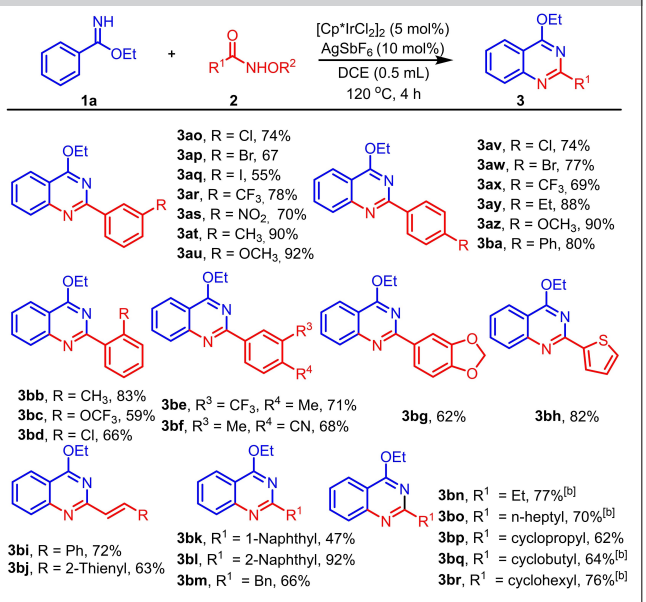
In order to investigate the universality of this method, the scope of *N*-alkoxyamides **2** was carefully examined (see Table 3). For *N*-alkoxyamides **2** bearing either electron-donating (–Me, –OMe) or -withdrawing groups ($–NO_2$, $–CF_3$) at the meta position of the phenyl ring, all reactions proceeded smoothly, and target products obtained in excellent yields (**3ar**–**3au**). The reaction tolerated many functional groups meaningful in synthetic chemistry, such as chlorine, bromine, and iodine (**3ao**–**3aq**). Such compatibility further enhances the synthetic practicality of this method. The reaction proceeded even when different functional groups occupied the para position (**3av**–**3ba**). A comparison of *meta*- and *para*-substituted substrates showed a slightly lower yield for substituents at the ortho position, but the cyclized product was still obtained in moderate to good yields (**3bb**–**3bd**). It is worth mentioning that disubstituted substrates also showed good tolerance and

Table 2. Substrate scope of the aryl imidates.[a]



[a] Unless otherwise noted, reactions were carried out with **1** (0.24 mmol), **2a** (0.2 mmol), $[Cp^*IrCl_2]_2$ (5 mol%) and $AgSbF_6$ (10 mol%) in DCE (0.5 mL).

Table 3. Substrate scope of *N*-alkoxyamide derivatives.[a]



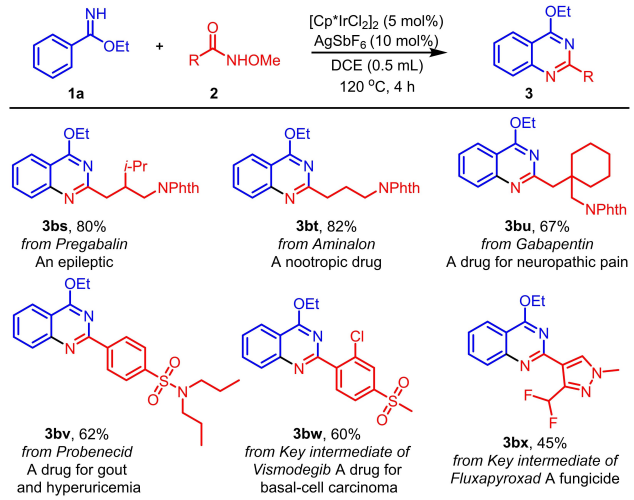
[a] Unless otherwise noted, reactions were carried out with **1a** (0.24 mmol), **2** (0.2 mmol), $[Cp^*IrCl_2]_2$ (5 mol%) and $AgSbF_6$ (10 mol%) in DCE (0.5 mL), R^2 = Me. [b] R^2 = Bn.

gave the desired products **3 be**–**3 bf** in moderate to good yields (68–71 %). In addition, substrates containing heterocycles, naphthalene rings, and olefins participated in the reaction and gave products **3 bg**–**3 bl** in 47–92 % yields. Furthermore, alkyl substituent substrates also yielded the desired products with yields of 62–77 % (**3 bn**–**3 br**).

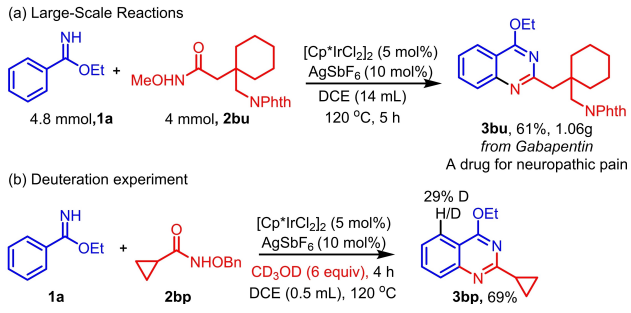
Different aminating reagents **2** transformed from several drugs such as Aminalon, Pregabalin, Gabapentin, and Probenecid were further investigated.[9b] As shown in Table 4, they coupled successfully with ethyl benzimidate **1 a** in the presence of Ir(III) via intermolecular C–H amidation/cyclization (**3 bs**–**3 bv**). Aminating reagents prepared by key intermediates of Vismodegib and Fluxapyroxad participated in this reaction smoothly and afforded target products in moderate to good yields (**3 bw**–**3 bx**).[9b] It is worth mentioning that products **3 bv** and **3 bw** have similar structures to Sildenafil[10] and Vardenafil[11] that are known for treating erectile dysfunction; this further emphasizes the importance of this method in promoting the development of new pharmaceutical drugs (Figure 1).

To demonstrate the practicicality of this synthetic method, we investigated the reaction of *N*-alkoxyamides **2 bu** and ethyl benzimidate **1 a** on a gram scale (Scheme 1a). To explore the

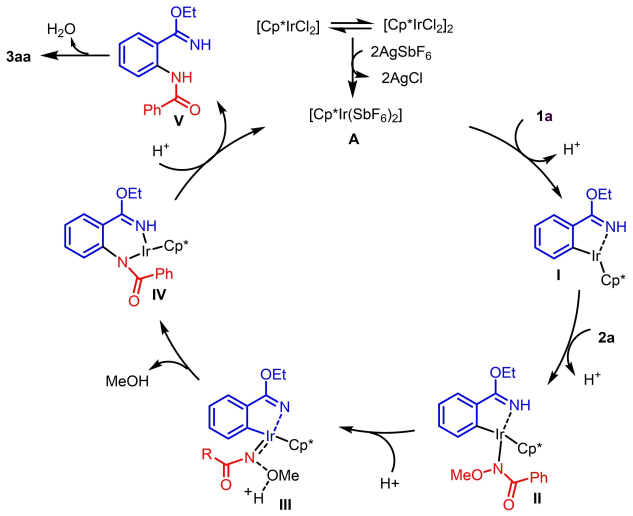
Table 4. Substrate scope of *N*-alkoxyamide derivatives.[a]



[a] Unless otherwise noted, reactions were carried out with **1 a** (0.24 mmol), **2** (0.2 mmol), $[Cp^*IrCl_2]_2$ (5 mol%) and $AgSbF_6$ (10 mol%) in DCE (0.5 mL).



Scheme 1. Scale up synthesis of **3 bu** and deuteration experiment.



Scheme 2. Possible reaction mechanism.

reaction mechanism, we carried out deuterium exchange reactions in the presence of CD_3OD. Those results showed that 29 % of the hydrogen atoms were replaced by deuterium, which indicated a reversible C–H activation process (Scheme 1b).

According to the mechanism proposed above and literature precedent,[9,12] Scheme 2 depicts a reasonable catalytic cycle. First, the anions from $[Cp^*IrCl_2]$ dissociate and exchange with $AgSbF_6$ to produce catalyst **A**. Subsequently, **1 a** attaches to **A** to produce an iridacyclic intermediate **I** via C–H activation. Coordination of aminating reagent **2 a** to **I** produces complex **II**. The protonic acid may activate the methoxy group, which would produce an complex **III**, followed by reductive elimination to give complex **IV**. Subsequently, intermediate **IV** releases intermediate **V**, which undergoes dehydrative cyclization to provide the quinazoline product **3 aa** and simultaneously regenerate the catalyst to complete the cycle.

Conclusion

In conclusion, we developed an unprecedented iridium-catalyzed C–H activation/cyclization to synthesize quinazoline compounds efficiently using ethyl benzimidate and *N*-alkoxyamides. This reaction has the advantages of wide substrate adaptability, short reaction times and no need for an inert atmosphere. In addition, some drug molecules smoothly converted into aminating reagents, reacted efficiently and afforded molecules with potential drug activity. Work to determine the pharmacological activities of those products is ongoing.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Bioactive compounds · C–H activation · Cyclization · Ir(III)-catalyzed · Quinazolines

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