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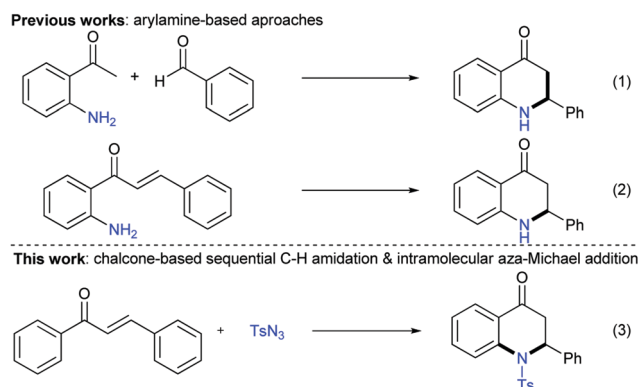
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# Synthesis of dihydroquinolinones *via* iridium-catalyzed cascade C–H amidation and intramolecular aza-Michael addition†

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An iridium-catalyzed annulation of chalcones with sulfonyl azides *via* cascade C–H amidation and intramolecular aza-Michael addition was developed, affording a variety of 2-aryl-2,3-dihydro-4-quinolones in moderate to good yields. This reaction features easy operation, readily available starting materials, and the cascade formation of two C–N bonds in one pot.

Quinolones are a class of compounds with a broad spectrum of antibiotic properties.<sup>1</sup> In particular, 2-aryl-2,3-dihydro-4-quinolones, namely azaflavanones, have attracted more attention due to their unique bioactivities such as antimalarial activity and cytotoxic activity against a panel of human tumor cell lines and potent cross-species microRNA inhibitors.<sup>2</sup> Besides, they also serve as key intermediates in the synthesis of many biologically active natural products.<sup>3</sup> Thus the synthesis of quinolones from readily available starting materials is highly desirable. Traditionally, the construction of the 2,3-dihydro-4-quinolone skeleton could be achieved *via* intermolecular Fries-type rearrangement of aryl  $\beta$ -lactams catalyzed by Brønsted or Lewis acids,<sup>4</sup> PPA-promoted intramolecular Friedel–Crafts acylation of 3-(arylamino)propanoic acids or esters,<sup>5</sup> Michael addition of 2-alkenoylanilines in the presence of appropriate bases,<sup>6</sup> and palladium-catalyzed intermolecular cyclizations.<sup>7</sup> In the case of 2-aryl-2,3-dihydroquinolin-4-ones, the condensation of *o*-aminoacetophenones and aryl aldehydes in the presence of certain organocatalysts was frequently employed (Scheme 1, eqn (1)).<sup>8</sup> In addition, intramolecular aza-Michael addition of *o*-aminochalcones was also utilized in the successful construction of this structure under the catalysis of transition-metals<sup>9</sup> or organocatalysts (Scheme 1, eqn (2)).<sup>10</sup> However, throughout the abovementioned approaches, either intermolecular or intramolecular reactions, odorous and vulnerable arylamines were used as essential substrates with limited substrate



Scheme 1 Approaches for the synthesis of 2-aryl-2,3-dihydro-4-quinolones.

scopes. As a result, more general, clean, and efficient methods are required for the direct construction of 2-aryl-2,3-dihydro-4-quinolone derivatives from readily available starting materials.

Direct C–H amidation was proved to be a convenient approach for C–N bond formation with high atom-economy.<sup>11</sup> In 2012, Chang pioneered direct C–H amidation employing sulfonyl azides as the N-sources with gaseous nitrogen as a clean by-product.<sup>12</sup> Subsequently, Chang's<sup>13</sup> and other groups<sup>14,15</sup> deeply demonstrated organic azide-involved direct C–H amidation as a reliable and efficient method for the construction of C–N bonds. Additionally, chalcones, which can be conveniently synthesized from aryl aldehydes and 1-arylethanones *via* Claisen–Schmidt condensation, are an important class of compounds that exhibit a broad range of biological activities (anticancer, antidiabetic, anti-HIV, and anti-inflammatory).<sup>16</sup> The  $\beta$ -H activation or *ortho*-C–H bond activation of chalcones was selectively achieved under transition-metal catalyzed conditions.<sup>17</sup> However, sequential *ortho*-C–H bond activation and aza-Michael addition in one pot has never been reported. In this paper, we aimed to accomplish the annulation of chalcones with sulfonyl azides *via* *ortho*-C–H bond amidation and then to fulfill the aza-Michael addition in one pot for the construction of 2-aryl-2,3-dihydro-4-quinolones with high atom- and step-economy (Scheme 1, eqn (3)).

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Table 1 Screening the optimized reaction conditions<sup>a</sup>

| Entry | Catalyst                                             | Additive           | Solvent | Yield <sup>b</sup> (%)            |
|-------|------------------------------------------------------|--------------------|---------|-----------------------------------|
| 1     | [Cp*RhCl <sub>2</sub> ] <sub>2</sub>                 | AgSbF <sub>6</sub> | DCE     | Trace                             |
| 2     | [Ru( <i>p</i> -cymene)Cl <sub>2</sub> ] <sub>2</sub> | AgSbF <sub>6</sub> | DCE     | Trace                             |
| 3     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                 | AgSbF <sub>6</sub> | DCE     | 26                                |
| 4     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                 | AgNTf <sub>2</sub> | DCE     | 30                                |
| 5     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                 | AgBF <sub>4</sub>  | DCE     | Trace                             |
| 6     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                 | AgNTf <sub>2</sub> | DCM     | 38 (49) <sup>b</sup>              |
| 7     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                 | AgNTf <sub>2</sub> | Toluene | 0                                 |
| 8     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                 | AgNTf <sub>2</sub> | MeCN    | Trace                             |
| 9     | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                 | AgNTf <sub>2</sub> | MeOH    | 7                                 |
| 10    | [Cp*IrCl <sub>2</sub> ] <sub>2</sub>                 | AgNTf <sub>2</sub> | DCM     | 63 <sup>c</sup> (77) <sup>d</sup> |

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol%), additive (20 mol%) in solvent (2 mL) at 100 °C for 12 h. <sup>b</sup> At 120 °C.

<sup>c</sup> Adding HOAc (1 equiv.), 120 °C. <sup>d</sup> Adding PivOH (1 equiv.), 120 °C.

To achieve our goals, we started to screen the reaction conditions for the cascade amidation and aza-Michael addition of chalcone (**1a**) with tosyl azide (**2a**) using Rh(III) as the catalyst and AgSbF<sub>6</sub> as the additive (Table 1, entry 1). However, only a trace amount of product was detected, even after we switched the catalyst to Ru(II) (Table 1, entry 2). To our delight, the desired product 2-phenyl-1-tosyl-2,3-dihydroquinolin-4(1H)-one (**3aa**) was obtained in 26% yield when catalyzed by [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (Table 1, entry 3). Encouraged by this result, other reaction parameters were then extensively investigated to further optimize the reaction. For example, AgNTf<sub>2</sub> was a better silver source than AgBF<sub>4</sub> (Table 1, entries 4 and 5). Other solvents such as DCM, toluene, acetonitrile, and methanol were tested, and the results indicated that DCM was the best choice (Table 1, entries 6–9). Increasing the temperature to 120 °C resulted in a higher yield (Table 1, entry 6). The yields increased remarkably after adding one equivalent amount of acid. Product **3aa** was isolated in 77% yield in the presence of pivalic acid (Table 1, entry 10).

After the establishment of the optimized reaction conditions, the substrate scope of this cascade amidation and aza-Michael addition reaction was investigated as listed in Fig. 1. As expected, chalcones with different substituents on aryls adjacent to alkenyl have little influence on the efficiency of this reaction, leading to the corresponding 2-aryl-2,3-dihydro-4-quinolone products in good yields (**3aa–3ka**, 85–65% yields). Electron donating groups, such as methyl, *tert*-butyl, and phenyl, or electron withdrawing groups, such as halo, nitro, and methoxycarbonyl, at either the *meta*- or *para*-position of phenyls, were all well tolerated. Next, the substituent influences on aryls adjacent to the carbonyls of chalcones were tested. Methyl, halo, and methoxycarbonyl at the *para*-position of phenyl all reacted smoothly to generate the products in good yields (**3la–3qa**, 74–55% yields). The tolerance of halo produced opportunities for further derivations (**3ea–3ha**, **3ma–3pa**, and **3ua**). In particular, iodo remains innocent under this Ir-catalyzed condition to produce **3pa** in 55% yield. Notably, steric hindrance had a negative influence on this reaction, for

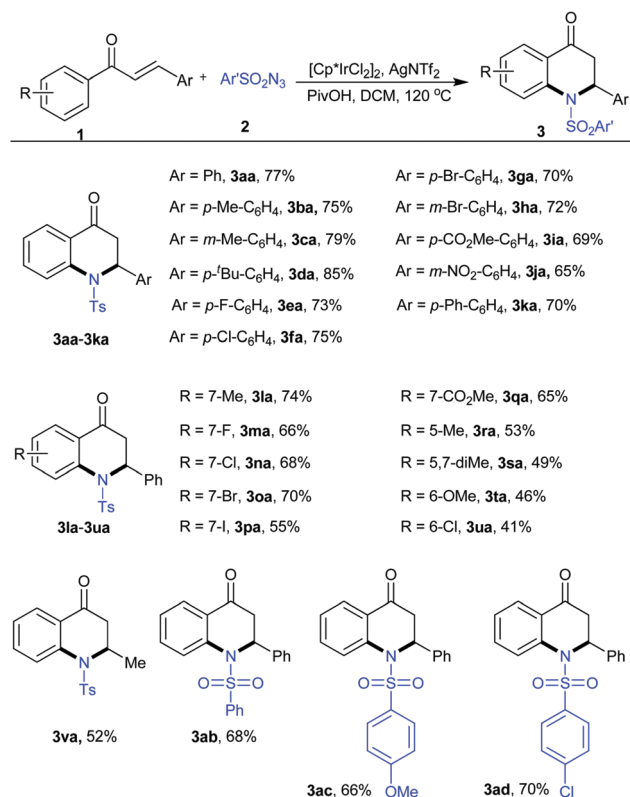
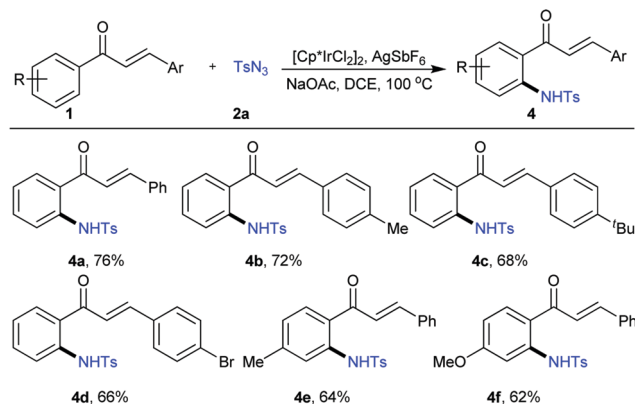


Fig. 1 Scope of the Ir-catalyzed cascade amidation and aza-Michael addition reactions.<sup>a</sup> <sup>a</sup>Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (5 mol%), AgNTf<sub>2</sub> (20 mol%), PivOH (1 equiv.) in DCM (2 mL) at 120 °C for 12 h, isolated yields.

chalcones with *ortho*-substituents generated the products in lower yields (**3ra** & **3sa**). In order to investigate the selectivity of this reaction, *meta*-substituted substrates **1t** and **1u** were subjected to the reaction, leading to the corresponding products in moderate yields with excellent regioselectivities (**3ta** & **3ua**). In addition, if the β-aryl was replaced with alkyl (**1v**), 2-alkyl-2,3-dihydroquinolin-4(1H)-one (**3va**) could be obtained in moderate yield. Other sulfonyl azides, such as benzenesulfonyl azide, 4-methoxybenzenesulfonyl azide, and 4-chlorobenzenesulfonyl azide, were also proved to be efficient N-sources, leading to the corresponding dihydroquinolin-4(1H)-ones in good to moderate yields (**3ab–3ad**).

Interestingly, if NaOAc was employed in the model reaction instead of pivalic acid, only *ortho*-amidation occurred, and no cyclisation product was detected at all. Other chalcones with different substituents all gave the amidation products in good to moderate yields in the presence of AgSbF<sub>6</sub> as the silver source (Fig. 2, **4a–4f**). This result was similar to Chang's.<sup>17f</sup>

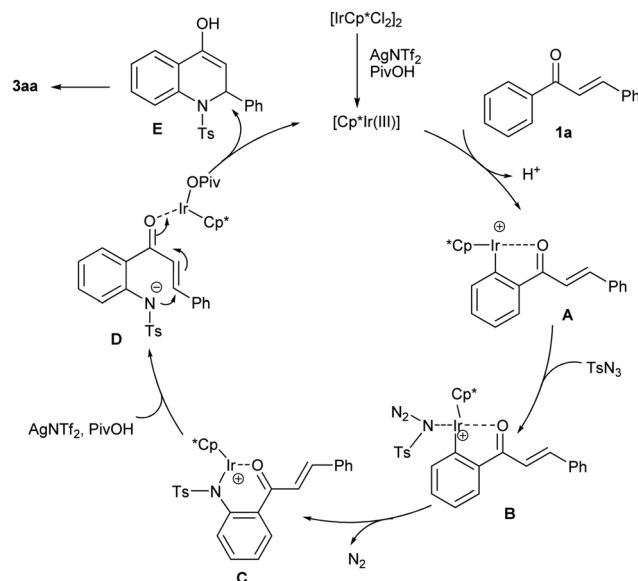
Control experiments were conducted to investigate the mechanism of this reaction as listed in Scheme 2. Product **3aa** could be isolated in 89% yield from **4a** catalyzed by [Cp\*IrCl<sub>2</sub>]<sub>2</sub> in the presence of AgNTf<sub>2</sub> (Scheme 2, eqn (a)). However, no product was formed in the absence of any transition-metal catalysts (Scheme 2, eqn (b)). The cyclisation could occur under the catalysis of either [Cp\*IrCl<sub>2</sub>]<sub>2</sub> or AgNTf<sub>2</sub>, while the yields were lower than that under the catalysis of the Ir–Ag system



**Fig. 2** Scope of the Ir-catalyzed cascade amidation and aza-Michael addition reactions.<sup>a</sup> Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), [Cp\*IrCl<sub>2</sub>]<sub>2</sub> (5 mol%), AgSbF<sub>6</sub> (20 mol%), NaOAc (1 equiv.) in DCE (2 mL) at 100 °C for 12 h, isolated yields.

(Scheme 2, eqn (c) & (d) vs. eqn (a)). These results indicated that the amidation product **4a** was the reaction intermediate and the metal-catalyst was essential for the aza-Michael addition step. Besides, AgNTf<sub>2</sub> may play an important role in the deprotonation process of **4a** to form the sulfamide anion with enhanced nucleophilicity for the following aza-Michael addition.

According to the mechanistic experiments and literature reports,<sup>13,15</sup> a possible mechanistic pathway is proposed in Scheme 3. First, the treatment of a dimeric iridium species with AgNTf<sub>2</sub> and PivOH generates the active Ir(III) catalyst, which induces the *ortho*-C–H bond cleavage of **1a** to produce cyclometalated Ir(III) complex **A**. Subsequently, the coordination of the tosyl azide to **A** forms Ir-species **B**. The following migratory insertion of **B** leads to intermediate **C** with the release of byproduct N<sub>2</sub>. Then, protodemetalation of **C** provides another Ir-coordinated intermediate, **D**. Finally, intramolecular



**Scheme 3** Proposed mechanism.

nucleophilic 1,4-addition of **D** gives compound **E** and regenerates the active Ir complex. Product **3aa** was formed from **E** after enol–keto tautomerization.

In summary, we have developed a cascade *ortho*-C–H amidation and intramolecular aza-Michael addition with chalcones and sulfonyl azides. A variety of 2-aryl-2,3-dihydro-4-quinolones with different substituents on aryls were obtained in moderate to good yields under standard conditions. This reaction features easy operation, readily available starting materials, and the cascade formation of two C–N bonds in one pot. This procedure represents an effective tool for the convenient synthesis of pharmaceutically promising heterocyclic compounds.

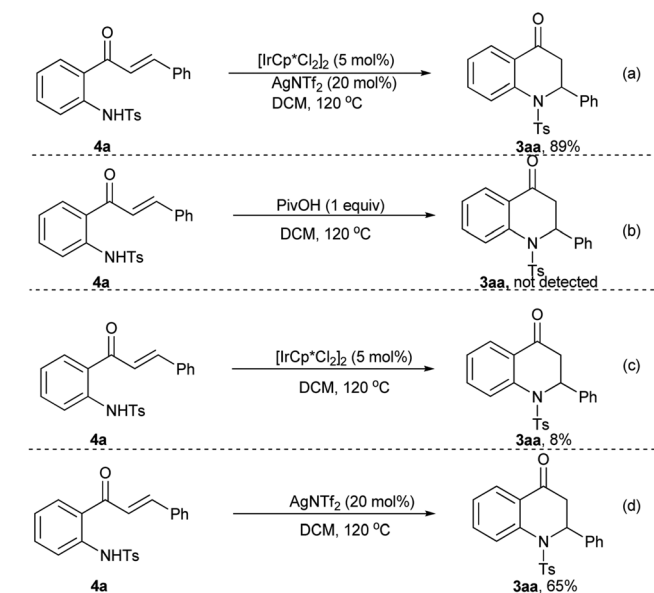
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## Conflicts of interest

There are no conflicts to declare.

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**Scheme 2** Mechanistic studies.

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