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Synthesis of indoles and quinazolines *via* additive-controlled selective C–H activation/annulation of *N*-arylamidines and sulfoxonium ylides†

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Selective synthesis of indole and quinazoline products was achieved through a precise control of the C–H activation/annulation by changing the additives from NaOAc to CuF_2/CsOAc. This strategy constructs indole and quinazoline scaffolds efficiently, and hence is of great interest in pharmaceutical, agricultural and chemical industries.

Transition-metal-catalyzed C–H activation has been extensively explored as it usually avoids the multistep preactivation of the starting materials providing an atom- and step-economical strategy for organic synthesis.[1] For instance, C–H activation/annulation, which has been one of the hottest topics in recent years,[2] does not only specifically functionalize the inert C–H bonds, but also forms a variety of cyclic compounds by coupling and cyclization with the introduced functional groups.

Indoles and quinazolines are two well-known classes of nitrogen-containing heterocyclic compounds that pose a broad-spectrum of biological activities and have been widely used in pharmaceutical, agricultural and chemical industries (Fig. 1).[3] Therefore, a more economical and environment-friendly synthetic strategy would be of great interest in the field. Among the published works, the formation of indoles was achieved mainly through the C–H activation of aniline derivatives with coupling reagents, such as alkene, alkyne and diazo (Scheme 1a).[4] On the other hand, quinazolines were mainly afforded *via* the C–H activation of benzimidates with amino reagents (dioxazolones and alkyl azides) or by the reactions of *N*-arylamidines with the "one-carbon coupling reagents" (C1 unit) like isonitrile and alkyne derivatives (Scheme 1b).[5]

Although the synthesis of indoles and quinazolines has been widely studied, most of the methods still have some drawbacks, such as the use of toxic and dangerous reagents (isonitrile, diazo, azide, *etc.*) and the unsatisfactory yields. Recently, sulfoxonium ylides have been widely used as a convenient and safe carbene precursor reagent in transition-metal-catalyzed C–H

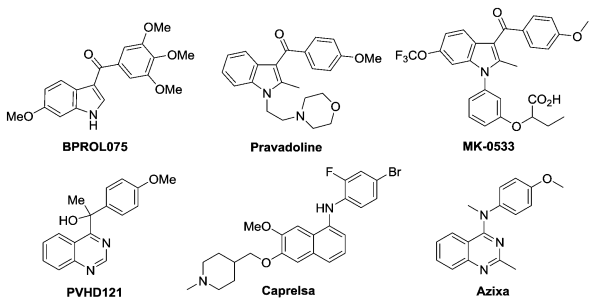
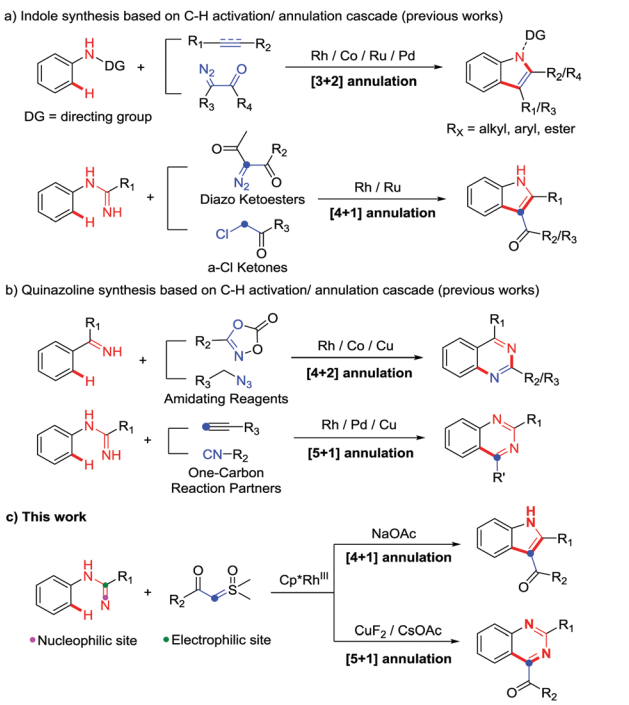


Fig. 1 Selected examples of bioactive indoles and quinazolines.



Scheme 1 C–H activation/annulation for the synthesis of indoles and quinazolines.

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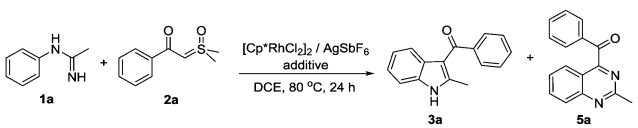
activation/annulation.[6] Many groups independently reported C–H activation/annulation cascade reactions of different directing groups (DGs) with sulfoxonium ylides as the C2 unit to obtain lactones, lactams, isoquinolines, azolopyrimidines, naphthols, *etc.*[6a–i] In addition, Kim's group recently used azobenzene with sulfoxonium ylide as the C1 unit to synthesize indazoles.[6j] Collectively, these results revealed that sulfoxonium ylide played an important role in C–H activation/annulation. As our group has been interested in C–H activation in recent years,[7] we were wondering whether it is possible to use *N*-arylamidines and sulfoxonium ylides to synthesize N-heterocycles through C–H activation/annulation. Herein, to answer this question, we report our most recent work on additive-controlled selective synthesis of indoles and quinazolines by using *N*-arylamidines and sulfoxonium ylides as the starting materials (Scheme 1c).

Initially, we selected *N*-phenylacetimidamide **1a** as a substrate to react with dimethyloxosulfonium benzoylmethylide **2a** using $[Cp^*RhCl_2]_2$ (5 mol%)/$AgSbF_6$ (20 mol%) as the catalyst. To our delight, (2-methyl-1*H*-indol-3-yl)(phenyl)methanone **3a** and 2-methyl-4-benzoylquinazoline **5a** were obtained in a 1 : 1 ratio with 62% total yield (Table 1, entry 1). Then, the relationship between additives and reaction results was explored (entries 2–11). It was shown that NaOAc as a base was obviously favored to generate the indole product **3a** (entry 3), while Cu salt, especially CuF_2, afforded quinazoline product **5a** mostly (entry 11). The effect of the solvent was also examined, and it turned out that DCE was the best (see the ESI†). Increasing the reaction temperature would cause serious side-reactions of ylide hence lowering the yield (see the ESI†). Increasing the amount of **2a** only improved the yield of **3a** (entries 12 and 13), and the formation of **5a** was favored by the oxygen environment (entry 14). In addition, as we found that CsOAc had a mild preference on **5a** (entry 5), we combined it with CuF_2 to see if it can further boost the yield. Fortunately, **5a** was obtained in 74% yield (entry 15).

With the optimized reaction conditions in hand, the C–H activation of imidamides was examined. Firstly, the substrate generality of indole products was explored, and the results are shown in Table 2. Unsubstituted *N*-phenylacetimidamide afforded **3a** with 78% isolated yield. The electron-donating, electron-withdrawing and halogen groups introduced into different positions of the benzene ring were fully tolerated (**3b–3q**), giving good to excellent yields (60–85%) for the indole products. Notably, when isopropyl, isobutyl, methoxyethyl and benzyl groups were introduced into *C*-alkyl imidamides, the reaction also successfully afforded desired products (**3r–3u**). Given the above results, it was found that the electron-donating groups, such as Me and OMe, and halogens on the phenyl were more favorable for this transformation than the electron-withdrawing groups including CF_3, nitro, acetyl and ester (**3g–3j**). In addition, the different substituting positions of the benzene ring affected the yields as well. The *para*-substitution was slightly better than the *meta*-, and the *meta*- was better than the *ortho*-. It was also found that when the imidamide was *meta*-monosubstituted by Me, both **3k** and **3′k** were produced in a ratio of 5 : 1. However, when Me was changed to F or Cl, only one regioisomer could be obtained (**3l** and **3m**). The difference in regioisomer formation may be the result of a combination of the steric effects and the electrical effects. Then, the change of sulfoxonium ylides was also investigated. When Me, MeO and halogen groups were attached to different positions on the benzene ring of sulfoxonium ylides, the reactions were fully tolerated (**4a–4i**), furnishing the desired products in good to excellent

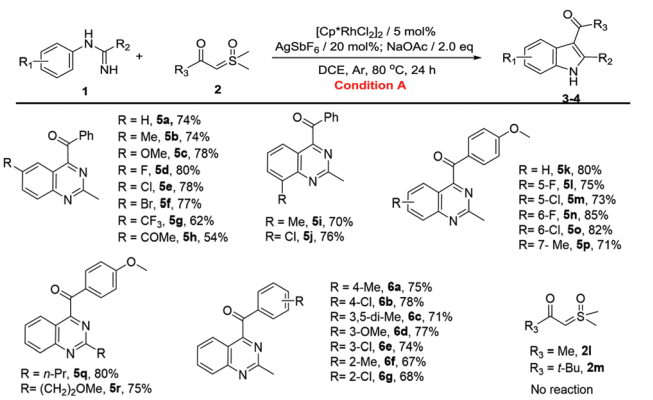
Table 1 Optimization of the reaction conditions[a]



Entry	Additive	Yield[b] (%) 3a	5a
1	—	33	29
2	HOAc	28	31
3	NaOAc	62	10
4	AgOAc	58	10
5	CsOAc	21	43
6	$CsCO_3$	27	35
7	$Cu(OAc)_2$	<5	51
8	$Cu(TFA)_2$	<5	42
9	$Cu(OTf)_2$	<5	45
10	$CuCl_2$	<5	31
11	CuF_2	<5	54
12[c]	**NaOAc**	**78**	**<5**
13[c]	CuF_2	<5	52
14[d]	CuF_2	<5	68
15[d,e]	**CuF_2/CsOAc**	**<5**	**74**

[a] Unless otherwise noted, all the reactions were carried out using *N*-phenylacetimidamide **1a** (0.20 mmol) and dimethyloxosulfonium benzoylmethylide **2a** (0.40 mmol) in the presence of $[Cp^*RhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mmol), additive (0.40 mmol) and DCE (1.0 ml) in a Schlenk tube, and the mixture was stirred at 80 °C for 24 h under Ar. [b] Isolated yield by chromatography on a silica gel. [c] Dimethyloxosulfonium benzoylmethylide **2a** = 0.60 mmol. [d] O_2 atmosphere. [e] CsOAc = 0.20 mmol.

Table 2 Synthesis of indoles[a]



[a] Reaction conditions: *N*-arylethanimidamides **1** (0.20 mmol), dimethyloxosulfonium benzoylmethylide **2a** (0.60 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mmol), NaOAc (0.40 mmol) and DCE (1.0 ml) in a Schlenk tube. The mixture was stirred at 80 °C for 24 h under Ar. Then, without any post processing, the reaction mixture was purified by column chromatography on a silica gel (eluent: PE/DCM = 1/1) to afford the desired product.

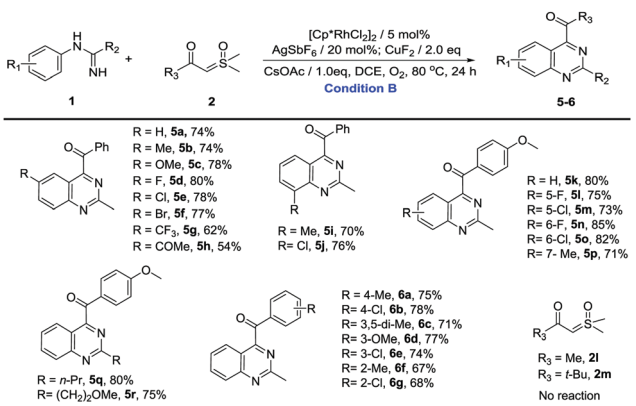
yields (66–82%). Notably, sulfoxonium ylides with MeO *ortho*-bisubstitution on the benzene ring had a yield of 66% only (**4i**). This may be due to the greatly increasing steric hindrance. When the benzene ring of ylide was changed to a naphthalene ring or a 1,3-benzodioxole ring, the reaction still proceeded smoothly and gave good yields (**4j** and **4k**). Once the benzene ring of the ylide was changed to Me (**2l**) or *t*-Bu (**2m**), no product was formed. It seemed that the aromaticity of the sulfoxonium ylide could be necessary in this reaction.

Then, we turned our attention to the synthesis of quinazolines (Table 3). Unsubstituted *N*-phenylacetimidamide gave 74% isolated yield of **5a**. The electron-donating, electron-withdrawing and halogen groups introduced into different positions of the benzene ring were fully tolerated (**5a–5p**), and the extension of the terminal carbon chain seemed to have no effect on the reaction (**5q** and **5r**), giving moderate to excellent yields (54–85%). Notably, when the benzene ring was *meta*-monosubstituted with Me, C–H activation took place in the C(6) site producing **5p**. However, when Me was changed to F or Cl, C–H activation took place in the C(2) site producing **5l** or **5m**. The results above may be the interaction of the steric effects and the electrical effects. Then, sulfoxonium ylides were investigated to further explore the substrate generality of quinazoline products. When Me, MeO and halogen groups were attached to different positions on the benzene ring of sulfoxonium ylides, the reactions were fully tolerated (**6a–6g**), furnishing the desired products in good yields (67–78%). Similarly, once the benzene ring of the ylide was changed to Me (**2l**) or *t*-Bu (**2m**), no product was found.

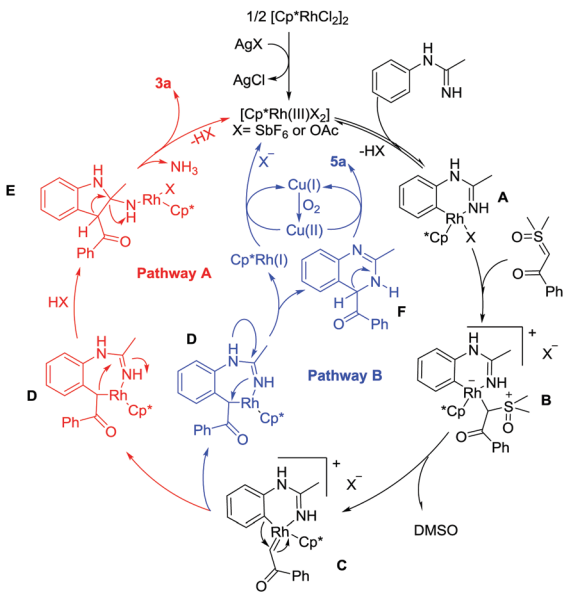
To gain mechanistic insight into the reaction, a series of experiments have been conducted (see the ESI†).[8] Based on the above results and previous related studies,[6g,9] a possible mechanism for this protocol is shown in Scheme 2. Cyclometalation of *N*-phenylacetimidamide **1a** and the active Rh(III) catalyst gives a rhodacyclic intermediate **A**. Coordination of dimethyloxosulfonium benzoylmethylide **2a** generates a Rh(III) alkyl species **B**, and the subsequent α-elimination of DMSO from **B** affords a reactive rhodium α-oxo carbene species **C**. Following the formation of **C**, two pathways may be possible. In pathway A, **C** is proposed to undergo migratory insertion of the Rh–C bond to generate a seven-membered rhodacyclic intermediate **D**. Intermediate **E** is then formed from unstable intermediate **D** by Rh–C(alkyl) migratory insertion into the C–N bond. Eventually, the final product **3a** is released from **E** by elimination of the active Rh(III) catalyst and one molecule of ammonia from **E** upon protonolysis and intramolecular protonolysis. In pathway B, the seven-membered rhodacyclic intermediate **D** is still generated. Then, the reductive elimination from intermediate **D** forms partially reduced quinazoline **F**. Subsequently, the oxidation of **F** affords the quinazoline product **5a**. On the other hand, the resulting Cp*Rh(I) can be reoxidized to the starting Rh(III) species by the action of Cu(II) and/or O_2 to complete the catalytic cycle.

It is noteworthy that this protocol really has many practical applications. For example, Pravadoline, a phase II drug, was recognized as a cannabinoid CB1 receptor agonist and has a strong analgesic effect (IC_{50} = 4.9 μM).[10] *N*-methylacetimidamide **1a** and dimethyloxosulfonium 4-methoxybenzoylmethylide **2c** were used to synthesize Pravadoline **9** in a shorter route yet with a higher yield, *i.e.* a total yield of 70%, in two steps (Scheme 3a). On the other hand, indole and quinazoline scaffolds have a broad-spectrum of biological activities. Based on a previous work,[11] we synthesized several indole compounds using our protocol (Scheme 3b), and we also choose several quinazoline compounds we synthesized (Scheme 3c). The anti-tumor activity of these indole and quinazoline compounds was evaluated. 3-Aroylindoles (**11a–11d**) all had excellent anti-tumor activity, while quinazoline products (**5n**, **5o**, **5q**, **5r**) put up a poor show. In comparison with **BPR-0L-075**, compounds **11b**, **11c** and **11d** displayed similar or greater growth inhibitory activities (see the ESI†).

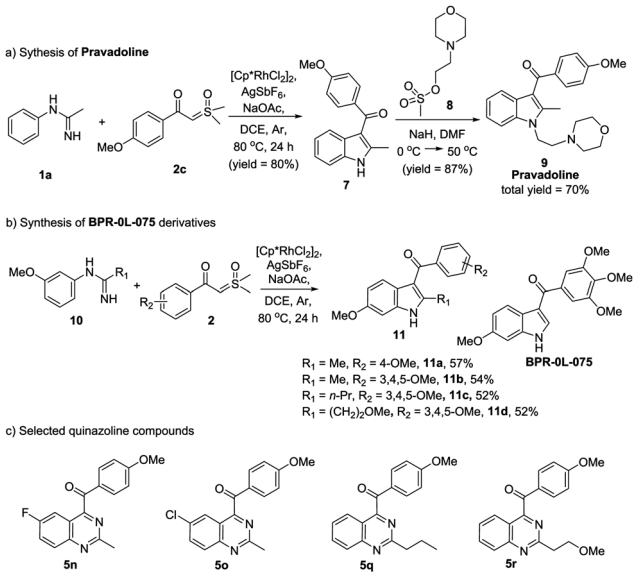
Table 3 Synthesis of quinazolines[a]



[a] Reaction conditions: *N*-arylethanimidamides **1** (0.20 mmol), dimethyloxosulfonium benzoylmethylide **2a** or **2c** (0.40 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.04 mmol), CuF_2 (0.40 mmol), CsOAc (0.20 mmol) and DCE (1.0 ml) in a Schlenk tube. The mixture was stirred at 80 °C for 24 h under O_2. Then, without any post processing, the reaction mixture was purified by column chromatography on a silica gel (eluent: PE/acetone = 50/1) to afford the desired product.



Scheme 2 Possible pathways of the C–H activation/cyclization.



Scheme 3 The practical applications of this protocol.

It is worth pinpointing that our highly efficient and scalable methodology for the synthesis of 3-aroylindoles and 4-aroylquinazolines will be extremely useful in discovering the novel anti-tumor compounds, and it may provide new ideas for drug design and synthesis.

In summary, we report the first example, to the best of our knowledge, of an additive-controlled selective C–H activation/annulation reaction of *N*-arylamidines and sulfoxonium ylides to selectively synthesize indoles and quinazolines. In this process, the additives were shown to play a key role in selectively controlling the [4+1] and [5+1] annulation. With the additive NaOAc, the reaction predominantly gave the indoles because of the [4+1] annulation. Changing the additives to CuF_2/CsOAc, the preference of the annulation was switched to [5+1], hence selectively affording the quinazoline products. Furthermore, this simple, rapid and efficient strategy may provide a new tool for the synthesis of N-heterocycles, hence facilitating chemical synthesis and drug design.

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Conflicts of interest

There are no conflicts to declare.

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