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Communication

Synthesis of aminoisoquinolines *via* Rh-catalyzed [4 + 2] annulation of benzamidamides with vinylene carbonate

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ABSTRACT

A new strategy is developed for the synthesis of 1-aminoisoquinoline derivatives. This Rh(III)-catalyzed [4 + 2] annulation reaction employs benzamidines as efficient directing groups and the vinylene carbonate as an acetylene surrogate. Additionally, the reaction features broad substrate scopes and good yields, only producing carbonate anion as byproduct.

During the past decades, transition-metal catalyzed cascade C-H activation/annulation reaction has clearly served as an efficient method in synthetic chemistry [1–6] to construct diverse heterocycles such as isoquinolines [7], quinazolines [8], naphthalenone [9], naphthols [10] and others [11–24]. And this method has been well explored by numerous chemists because of its simple operation, fewer synthetic steps, high atom economy and high regioselectivity.

On the other hand, 1-aminoisoquinolines are frequently found in many drug molecules (Fig. 1) and exhibit a wide range of biological and pharmaceutical activities [25–31]. Therefore, straightforward strategy to access 1-aminoisoquinolines has intensively intrigued the scientists. According literatures, many methods have been reported including the coupling reaction of 1-aminoisoquinoline with phenylboronic acid [32], the transformation of 1-chloroisoquinoline with amine [33–35], and the amination between isoquinoline-*N*-oxide with amines [36–42], phenyl isothiocyanate [43]. Besides, benzamidines are efficient directing groups [44–53], which have been widely employed for the construction of 1-aminoisoquinolines derivatives *via* C-H activation/annulation adopting different C2 synthons, such as α-OMs/OTs acetophenone [54], diazo compounds [55–57], allyl carbonates [58], alkynes [59,60] and sulfoxonium ylides (Scheme 1a) [61,62]. However, all of these transformations only provided the aminoisquinolines with R_2 or R_3 (phenyl or alkyl), and the construction of nonsubstituted aminoisquinoline skeletons (R_2, R_3 = H) were seldom disclosed through C-H activation.

Recently, vinylene carbonate, featuring higher operational security and commercial availability as acetylene surrogate, has been involved in the transition-metal-catalyzed C(sp^2)-H activation reactions [63–66] by extruding a carbonate anion (Scheme 1b). In these cases, heterocyclic structures such as isoquinolinones and isocoumarins, have been successfully and efficiently synthesized utilizing vinylene carbonate as a new C2 synthon under Co(III) or Rh(III) catalysis with *N*-methoxybenzamide [67] or benzoic acid [68]. In this regard, we herein demonstrate a facile method to generate nonsubstituted aminoisoquinolines derivatives by a Rh(III)-catalyzed cascade C-H activation/annulation reaction using benzimidamides with vinylene carbonate (Scheme 1c).

We commenced the reaction of Rh(III)-catalyzed [4 + 2] annulation reaction with *N*-(*tert*-butyl)benzimidamide (**1a**) and vinylene carbonate (**2a**) as model substrates. To our delight, we obtained the expected aminoisoquinolines products in 20% yields by employing $[Cp^*RhCl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) as catalytic system in 1,2-dichloroethane at 100°C for 24 h under argon atmosphere (Table 1, entry 1). Initially, the yields of aminoisoquinolines did not increase when replacing the Rh catalyst with other metal catalysts (entries 2 and 3). Then several sliver salts were investigated, among which AgOTf gave the superior result compared with $AgSbF_6$, $AgBF_4$ and AgOTs (entries 4–6). In order to

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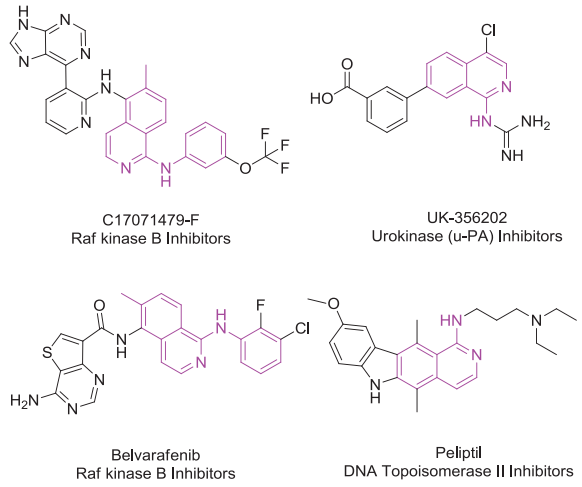
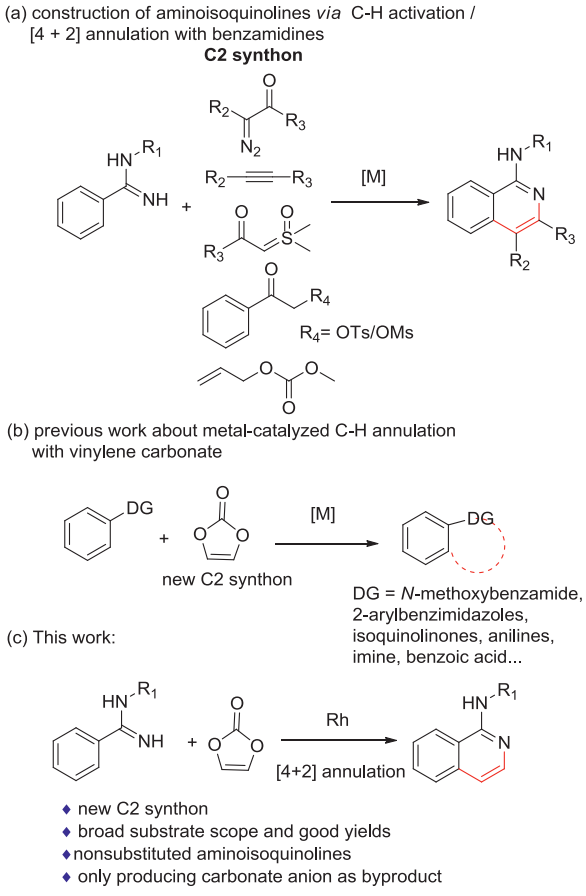


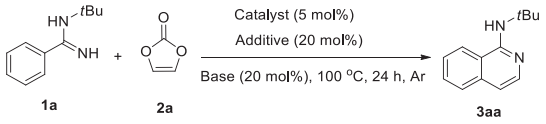
Fig. 1. Selected examples of bioactive aminoisoquinolines.



Scheme 1. Synthesis of aminoisoquinolines and other heterocycles *via* C-H activation/annulation.

further increase the yield, different bases were screened including NaOAc, KPF_6, K_2CO_3, KOPiv, and the results revealed that KOPiv was the best base for this reaction (entries 7–10). Finally, the use of toluene significantly increased the yield to 79%, which revealed solvents have a significant impact on the conversion (entries 11–13). In conclusion, the optimal conditions are shown as follows: the reaction proceeded in 79% yield under $[Cp^*RhCl_2]_2$ (5 mol%) and AgOTf (20 mol%), using KOPiv (20 mol%) as additives in Tol (2.0 mL) at 100 °C for 24 h under Ar.

Table 1
Optimization of reaction conditions.[a]

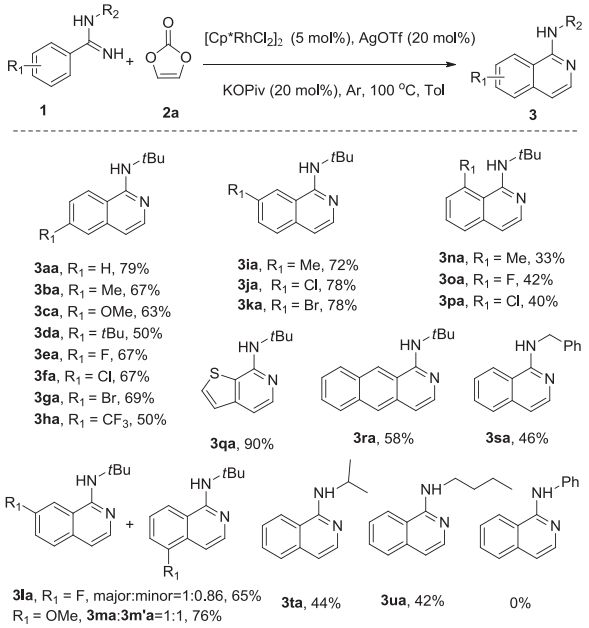


Entry	Catalyst	Additive	Base	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	-	DCE	20
2	$[Rh(cod)Cl]_2$	$AgSbF_6$	-	DCE	10
3	$[Ir(cod)Cl_2]_2$	$AgSbF_6$	-	DCE	Trace
4	$[Cp^*RhCl_2]_2$	$AgBF_4$	-	DCE	15
5	$[Cp^*RhCl_2]_2$	AgOTs	-	DCE	17
6	$[Cp^*RhCl_2]_2$	AgOTf	-	DCE	30
7	$[Cp^*RhCl_2]_2$	AgOTf	NaOAc	DCE	40
8	$[Cp^*RhCl_2]_2$	AgOTf	KPF_6	DCE	45
9	$[Cp^*RhCl_2]_2$	AgOTf	K_2CO_3	DCE	10
10	$[Cp^*RhCl_2]_2$	AgOTf	KOPiv	DCE	50
11	$[Cp^*RhCl_2]_2$	AgOTf	KOPiv	DMF	60
12	$[Cp^*RhCl_2]_2$	AgOTf	KOPiv	Cyclohexane	74
13	$[Cp^*RhCl_2]_2$	AgOTf	KOPiv	Toluene	79

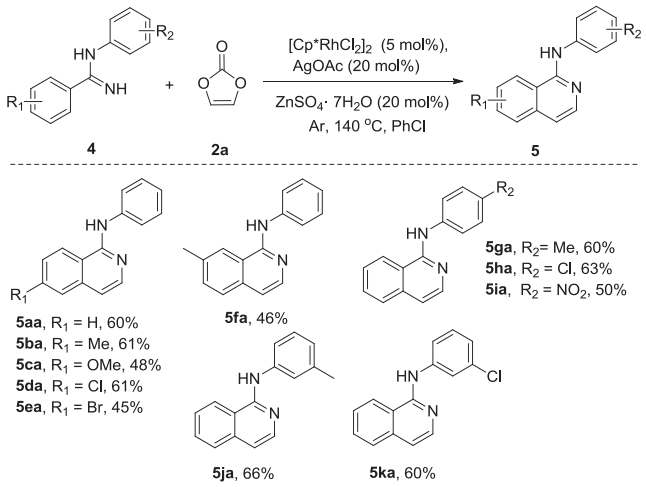
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (5 mol%), additive (20 mol%), base (20 mol%), solvent (1.5 mL), under Ar, 100 °C, 24 h.
[b] Isolated yields.

With the optimized conditions in hand, we started to investigate the scope and generality of benzamidines derivatives for the [4 + 2] annulation reactions. Generally, benzamidines bearing electron-donating (Me, OMe, *t*-Bu) and electron-withdrawing groups (F, Cl, Br) on the benzene ring could generate aminoisoquinolines derivatives (Scheme 2, **3aa-3ha**) smoothly by reacting with vinylene carbonate in moderate to good yields. As shown in Scheme 2, it was obvious that the yields of the transformation decreased dramatically to 33%–42% for *ortho*-substituent substrates (**3na-3pa**), which indicated that the transformation was tremendously influenced by steric hindrance effect. Besides, it was interesting to note that the substrates with diverse groups at the *meta* position demonstrated higher efficiencies than that at the *para* position on the whole. In addition, *meta*-methyl-, *meta*-cholro- and *meta*-bromo-substituted benzamidines preferred the site with less hindrance (**3ia-3ka**), while *meta*-methoxyl- and *meta*-fluoro-substituted reactants gave the two regioselective products (**3la-3ma**). Delightfully, the product was isolated in 90% yields when reactant with a thiophene ring was used. Moreover, substituent with naphthalene was also suitable for the reaction, albeit in a 58% yield. Furthermore, when *tert*-butyl is replaced by other alkyl groups such as benzyl, isopropyl and *n*-butyl, this cascade procedure could also convert to generate corresponding products in 42%–46% yields (**3sa-3ua**). However, the reaction failed to work when *N*-phenylbenzimidamide was added.

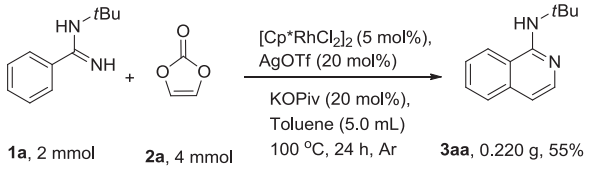
Due to the inert reactivity of *N*-phenylbenzimidamide, a series of reaction conditions were examined for realization of the conversion by employing vinylene carbonate (see Supporting information for details). Fortunately, we obtained the expected *N*-



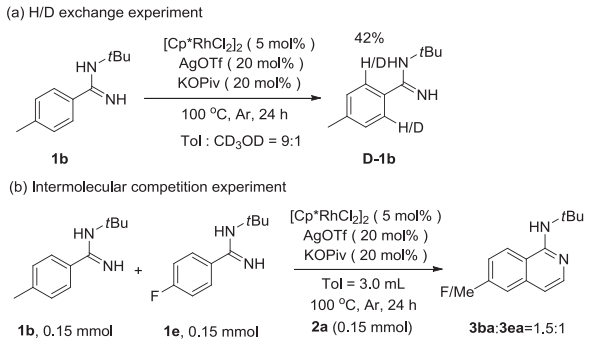
Scheme 2. Substrate scope of benzamidines. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), AgOTf (20 mol%), KOPiv (20 mol%), Toluene (1.5 mL), Ar, 100 °C, 24 h.



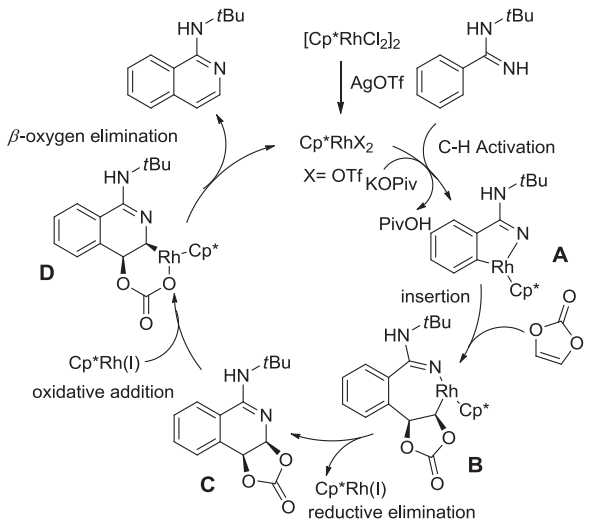
Scheme 3. Substrate scope of *N*-phenylbenzimidamides.



Scheme 4. Ten-fold-scale synthesis of aminoisoquinolines.



Scheme 5. Mechanistic studies.



Scheme 6. Plausible reaction mechanism.

phenylisoquinolin-1-amine successfully and confirmed the optimal conditions that the reaction proceeded in 60% yield with $[Cp^*RhCl_2]_2$ (5 mol%), AgOAc (20 mol%) and $ZnSO_4 \cdot 7H_2O$ (20 mol%) as catalytic system in chlorobenzene (2.0 mL) at 140°C for 24 h under Ar (Scheme 3). The electron-donating and electron-withdrawing groups were all compatible in 45%–66% yields without obvious electrical effect. Unfortunately, when the benzene ring was replaced by thiophene ring or naphthalene, we did not observe obvious products.

In order to explore whether the strategy could be applied for large scale, we enlarged the amount of **1a** (2 mmol) and **2a** (4 mmol) under the optimized conditions (Scheme 4). The result disclosed the transformation was less efficient in the yield of 55%.

To further explore the experimental mechanism, we completed some mechanistic experiments. The H/D exchange experiment was carried out by using **1b** with CD_3OD at 100 °C for 2 h, which showed that 42% deuterium incorporation was estimated at ortho-position by ^1H NMR indicating C-H bond cleavage of the transformation was reversible (Scheme 5a). When equimolar amounts of **1b** and **1e** were added in intermolecular competition experiment, the **3ba** and **3ea** were obtained in a ratio of 1.5:1, which indicated that electron-donating group was more effective (Scheme 5b).

Based on the above experiments and related literature, a plausible mechanism is presented in the Scheme 6. First, benzamidine transforms into a rhodacyclic intermediate **A** by C-H activation. Subsequently, the insertion of **2a** with intermediate **A** results in the formation of seven-member intermediate **B**. Then, intermediate **B** undergoes reductive elimination to generate intermediate **C** releasing the Cp*Rh (I). The rhodium complexe **D** is obtained from oxidative addition of intermediate **C** and Cp*Rh (I). Finally, the rhodium complexe **D** generates aminoisoquinoline with the formation of the carbonate anion through β-oxygen elimination.

In conclusion, we developed a novel method to construct aminoisoquinolines derivatives *via* Rh(III)-catalyzed C-H activation/annulation by coupling benzamidines with vinylene carbonate as an acetylene surrogate. In this work, we realized the transformations of phenyl and alkyl-substituted benzamidines in good to moderate yields under different conditions, which was applied for larger scale.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper .

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.04.058.

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