Rh(III)-Catalyzed C–H Amidation of 2-Arylindoles with Dioxazolones: A Route to Indolo[1,2-*c*]quinazolines

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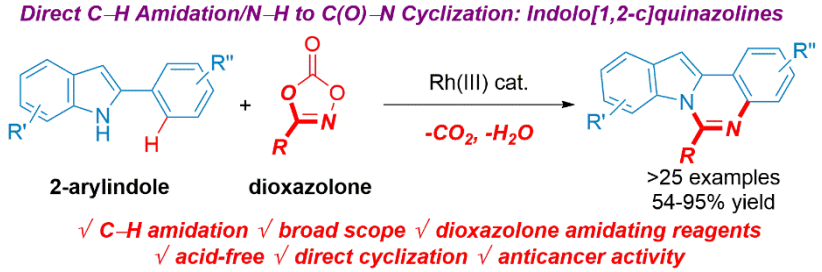
Supporting Information



ABSTRACT: Rhodium(III)-catalyzed C–H amidation of 2-arylindoles with dioxazolones for the synthesis of indolo[1,2-*c*]quinazolines is reported. The reaction is compatible with a wide range of electronically-diverse 2-arylindoles and dioxazolones, providing indolo[1,2-*c*]quinazolines in high to excellent yields. Most notably, the combination of this Rh-catalyzed C–H amidation and intramolecular N–H/N–C(O) cyclization enables the most straightforward direct route to indolo[1,2-*c*]quinazolines to date. Mechanistic studies and evaluation of antitumor activity of these high value heterocycles are disclosed.

Indolo[1,2-*c*]quinazolines are an important class of indole-fused heterocycles that are widely represented in natural products, bioactive compounds and organic photoluminescent devices (Figure 1).[1,2] A classic method for the synthesis of indolo[1,2-*c*]quinazolines involves intramolecular condensation of 2-ortho-aminoarylindoles with carbonyl equivalents; however, this approach is inefficient, requires indole prefunctionalization and is limited in terms of atom- and step-economy (Scheme 1A).[3,4] Given our interest in amide bonds,[5,6] we postulated that a direct route to this high value scaffold should be feasible utilizing C–H amidation of broadly available 2-arylindoles[7] (Scheme 1B). We hypothesized that the capacity of N–H indoles to form amidorhodium[8] species followed by C–H amidation[9,10] together with a proximity driven electrophilic cyclization of the aromatic amide[11] might enable an expedient route to indolo[1,2-*c*]quinazolines. If successful, this would provide the most straightforward catalytic route to this high value heterocyclic scaffold to date.[12–15]

Considering the synthetic importance of indolo[1,2-*c*]quinazolines, methods for the improved synthesis of this heterocycle have attracted a great deal of attention. For example, the studies by Zhang demonstrated that indolo[1,2-c]quinazolines can be accessed by Cu-catalyzed sequential amination (X = Br, I)/aerobic oxidative cyclization of 2-(2-haloaryl)-1*H*-indoles (Scheme 1C).[12] Fan reported Cu-catalyzed cascade amination/condensation/oxidative cyclization of 2-(2-bromoaryl)-1*H*-indoles (Scheme 1C).[13] More recently, a Cu-catalyzed electrophilic amidation of 2-(2-amidoaryl)-1*H*-indoles was reported, wherein the Cu-catalyst acts as an *O*-coordinating Lewis acid to facilitate the cyclization.[14] However, these methods start from ortho-substituted 2-arylindoles[15] and are limited by atom-economy.[3] In sharp contrast, a direct synthesis of indolo[1,2-*c*]quinazolines by C–H amidation/N–H to N–C(O) condensation of 2-arylindoles would provide an attractive platform for generating diversity of this important heterocycle.

In the past decade, group-directed C–H functionalization has been broadly developed for building valuable C–C and C–heteroatom bonds.[16] Chang[17] and Li[18] have reported dioxazolones as electrophilic –NC(O)R sources for direct

C–H amidation reactions.[19] These highly reactive amidating reagents have numerous advantages that permit introducing valuable amide bonds

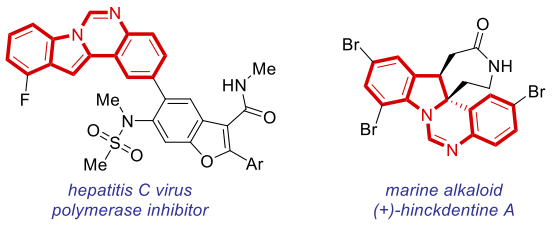
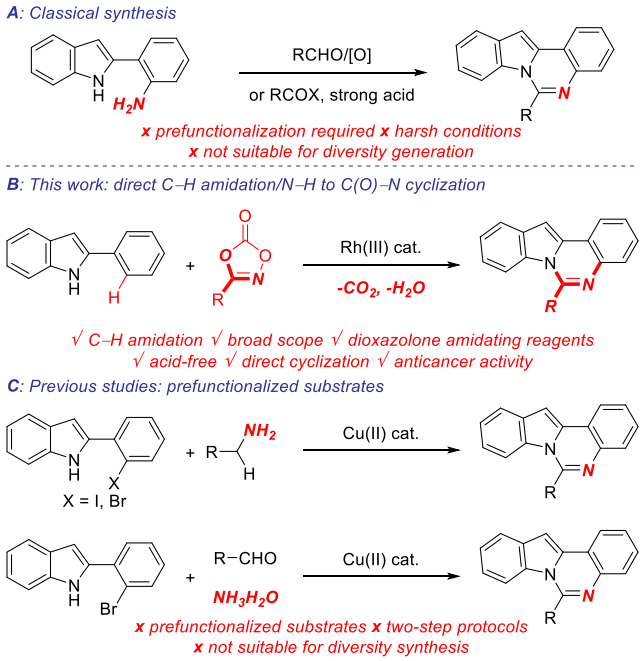


Figure 1. Examples of indolo[1,2-*c*]quinazolines.

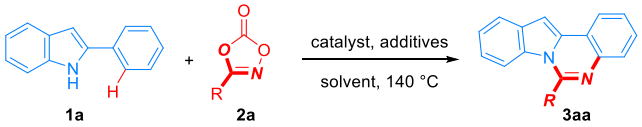
Scheme 1. Previous studies and this work



by leveraging high affinity of the Lewis basic nitrogen atom with facile nitrenoid formation.[20] The amidation step could be combined with the subsequent cyclization for the synthesis of heterocycles, such as quinazolines,[21] benzimidazoles,[22] quinazolinone,[23] or quinazoline N-oxides.[24,25] Herein, we report Rh(III)-catalyzed synthesis of indolo[1,2-*c*]quinazolines by a direct C–H amidation of 2-arylindoles with dioxazolones (Scheme 1B). The method enables the most straightforward diversity generating direct route to indolo[1,2-*c*]quinazolines and is characterized by high atom- and step-economy with H_2O and CO_2 formed as by-products.

We commenced our studies by investigating the reaction between 2-phenyl-1*H*-indole (**1a**) and 3-phenyl-1,4,2-dioxazol-5-one (**2a**) to optimize the reaction conditions (Table 1). The reaction using $[Cp^*RhCl_2]_2$ (5 mol%) and $AgSbF_6$ (25 mol%) as the catalytic system and CsOAc (25 mol%) as a basic additive in DCE at 140 °C afforded the desired C–H amidation/N–H to N–C(O) cyclization product in 62% (entry 1). Among other catalytic systems, including $[Cp^*RhCl_2]_2$, $[Ru(p\text{-cym})Cl_2]_2/AgSbF_6$, $[Cp^*CoCOI_2]/AgSbF_6$ and $Pd(OAc)_2$ (entries 2-5) only Co(III) afforded a trace of the desired product (<5%). A solvent screen revealed that DCE is optimal (entries 6-8). We could further improve the yield of (**3aa**) to 85% by using LiOAc as an additive (25 mol%) (entry 9), whereas other additives (NaOAc, KOAc, $Cu(OAc)_2$) were ineffective (entries 10-12). $[Cp^*Ir(III)Cl_2]_2$ is not a competent catalyst for the reaction, (recovery of the starting material). The C-H amidation does not proceed at 80 °C (recovery of the starting material).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	additive	solvent	yield (%)
1	$[Cp^*RhCl_2]_2/AgSbF_6$	CsOAc	DCE	62
2	$[Cp^*RhCl_2]_2$	CsOAc	DCE	<5
3	$[Ru(p\text{-cym})Cl_2]_2$/ $AgSbF_6$	CsOAc	DCE	<5
4	$[Cp^*CoCOI_2]/AgSbF_6$	CsOAc	DCE	<5
5	$Pd(OAc)_2$	CsOAc	DCE	<5
6	$[Cp^*RhCl_2]_2/AgSbF_6$	CsOAc	dioxane	<5
7	$[Cp^*RhCl_2]_2/AgSbF_6$	CsOAc	toluene	12
8	$[Cp^*RhCl_2]_2/AgSbF_6$	CsOAc	DMF	<5
9	$[Cp^*RhCl_2]_2/AgSbF_6$	LiOAc	DCE	85
10	$[Cp^*RhCl_2]_2/AgSbF_6$	NaOAc	DCE	44
11	$[Cp^*RhCl_2]_2/AgSbF_6$	KOAc	DCE	<5
12	$[Cp^*RhCl_2]_2/AgSbF_6$	$Cu(OAc)_2$	DCE	<5

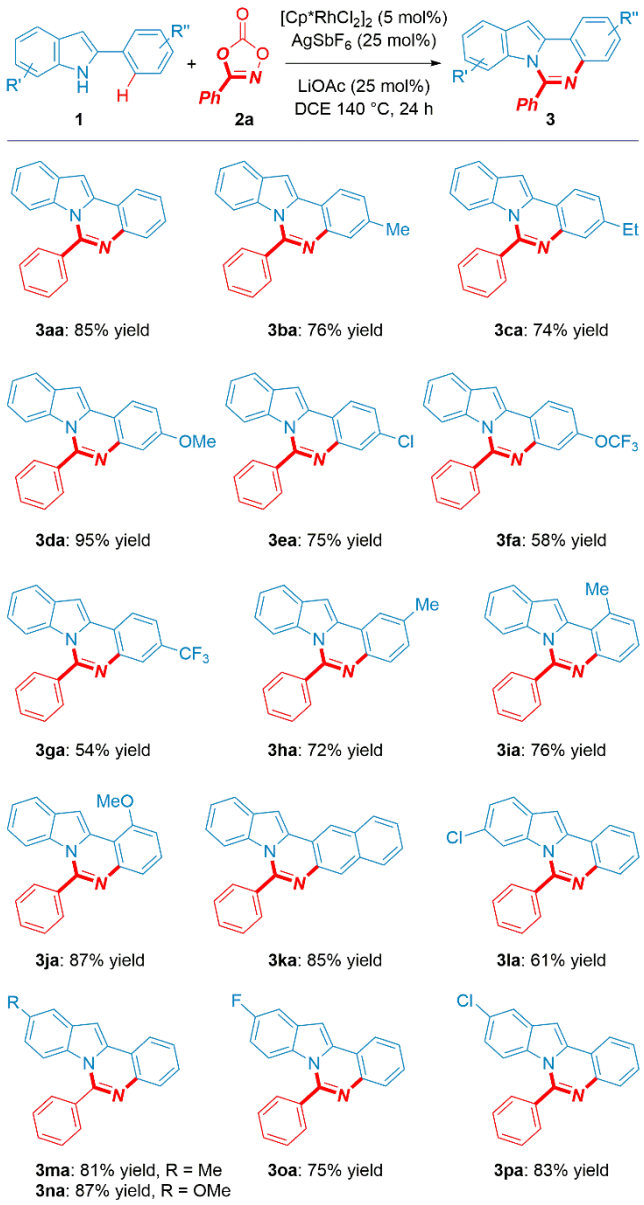
[a]Conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), catalyst (5 mol%), additive (25 mol%), solvent (0.10 M), 140 °C, 24 h.

With the optimized conditions in hand, the scope of the reaction was next investigated (Scheme 2). As shown, the scope of 2-aryl-1*H*-indole substrates is quite broad and accommodates a broad range of electron-donating (**3ba-3da)**, electron-withdrawing (**3ea-3ga**) and halide groups (**3ea**) at the para position of the 2-aryl ring; however, 2-aryl-1*H*-indoles bearing electron-withdrawing groups gave lower yields (*vide infra*). It is noteworthy that a single regioisomer was formed using a meta-substituted substrate (**3h**). Furthermore, the reaction was equally efficient when sterically-hindered ortho-substituted 2-aryl-1*H*-indoles were used (**3ia-3ja**). The scope could be further extended to a napthyl-substituted indole, furnishing a conjugated pentacyclic benzo[*g*]indolo[1,2-*c*]quinazoline (**3ka**). Importantly, 2-phenyl-1*H*-indoles bearing electron-donating (**3ma-3na**) as well as halide groups (**3la, 3oa-3pa**) at the 5- or 6-position of the indole ring could also be used to rapidly generate the indolo[1,2-*c*]quinazoline scaffold.

To further investigate the substrate scope, we subjected a range of dioxazolones to the reaction with 2-phenyl-1*H*-indole (Scheme 3). Pleasingly, we found that both 3-alkyl and 3-aryl substituted 1,4,2-dioxazol-5-one reagents could be used for the synthesis of indolo[1,2-*c*]quinazolines. The reactions with alkyl dioxazolones afforded the products in excellent yields (**3ab-3ac**). 3-Aryl-1,4,2-dioxazol-5-ones containing electron-donating (**3ad-3ae**), polyaromatic

(**3af**), electron-withdrawing (**3ag**) and halide groups (**3ah-3aj**) worked well to afford functionalized indolo[1,2-*c*]quinazolines. The functional group tolerance for an aryl bromide is noteworthy (**3aj**). Finally, we delighted to find that the reaction of 3,5-dimethoxyphenyl-1,4,2-dioxazol-5-one afforded **3ak** in 68% yield. This product shows excellent antibacterial activity, highlighting the practical utility of the current protocol. Typically, we have not observed side reactions in this method. At the present stage of reaction development 4-nitrophenyl dioxazolone has not been tested. Future work will focus on expanding the scope of C-H amidation processes.

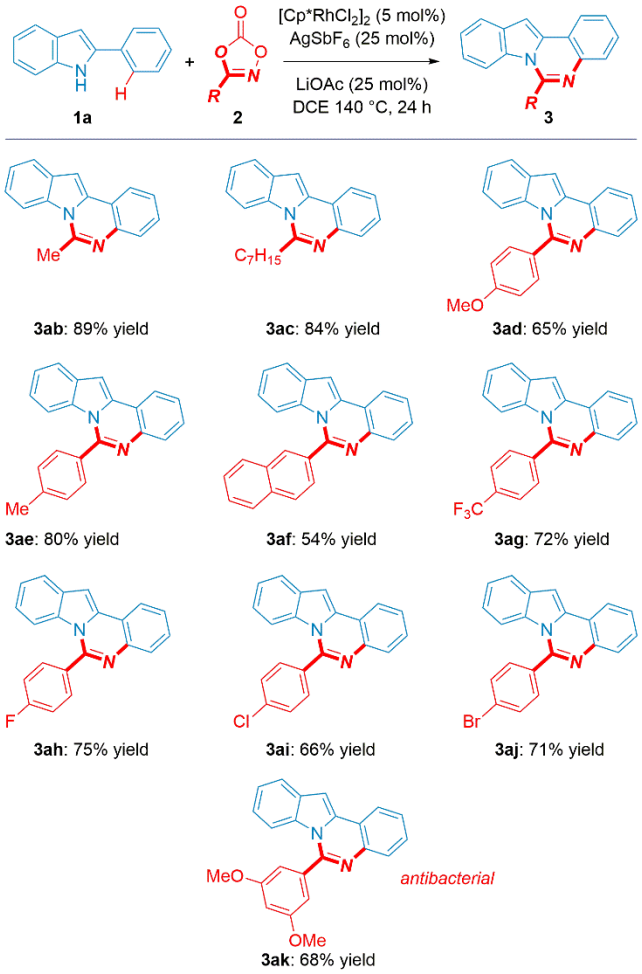
Scheme 2. Scope of 2-Aryl-1*H*-Indole Substrates[a,b]



[a]Conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (25 mol%), LiOAc (25 mol%) DCE (0.10 M), 140 °C, 24 h. [b]Isolated yields. See Supporting Information (SI) for details.

We conducted experiments to gain insight into the reaction mechanism (Scheme 4). Intermolecular competition studies between differently substituted 2-aryl-1*H*-indoles revealed electron-rich arenes to be inherently more reactive (Scheme 4A). Furthermore, electron-rich 2-phenyl-1*H*-indoles are inherently more reactive than their electron-deficient counterparts (Scheme 4B), while electron-deficient arenes are transferred preferentially from the dioxazolone amidating reagent (Scheme 4C). Moreover, radical inhibition studies revealed decreased yields of the amidation product (Scheme 4D). Overall, these studies are consistent with an electrophilic C–H activation mechanism, with the N–H to C(O)–N cyclization facilitated by electron-rich indoles.

Scheme 3. Scope of 1,4,2-Dioxazol-5-one Substrates[a,b]



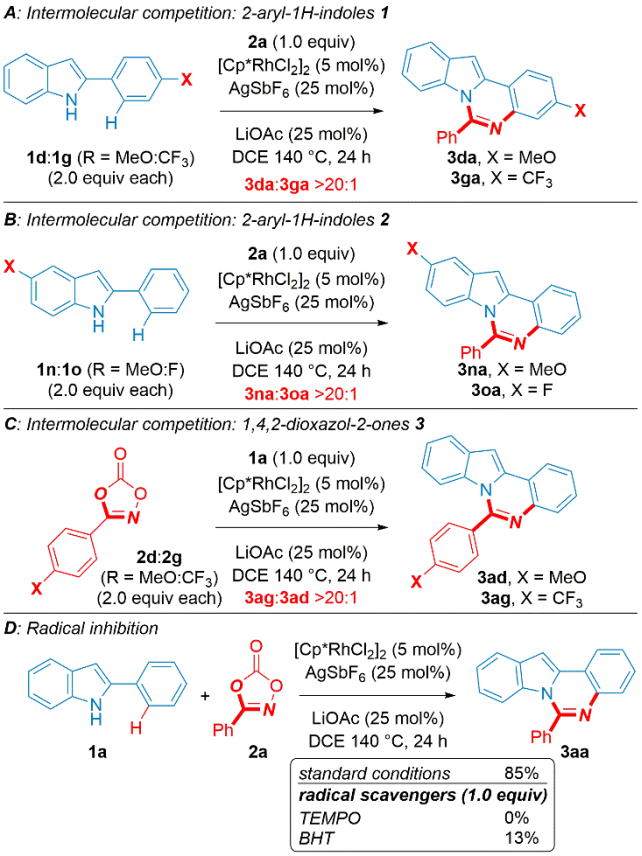
[a]Conditions: **1a** (1.0 equiv), **2a** (1.2 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (25 mol%), LiOAc (25 mol%) DCE (0.10 M), 140 °C, 24 h. [b]Isolated yields. See Supporting Information (SI) for details.

A plausible reaction mechanism is shown in Scheme 5. The formation of an amidorhodium N–Rh(III) species and subsequent C–H activation gives a five-membered rhodacycle **4**.[9] Coordination of dioxazolone and CO_2 extrusion gives a highly reactive Rh-imido intermediate **5**.[18] Migratory insertion and cyclization gives the indolo[1,2-*c*]quinazoline product **3** and regenerates the catalyst. The electrophilic cyclization onto the amide is likely facilitated

by a N-/O-Rh-migration to increase the amide bond electrophilicity.[11]

The potential of the present method in the synthesis of complex indolo[1,2-*c*]quinazolines is highlighted in cytotoxic studies (Table 2). Intrigued by the unique capacity of this valuable heterocyclic scaffold to act as a privileged synthon in drug discovery, we tested the synthesized products against human prostate cancer cells (PC3), human lung cancer cells (A549) and human Michigan cancer foundation cells (MCF-7) (see SI for details).[26] As shown, the compounds **3pa**, **3ad**, **3ag** and **3ak** displayed promising growth inhibition of A549 cells (**3ag**: IC50 = 30.7 uM). The results demonstrate that indolo[1,2-c]quinazolines could represent a new class of cancer growth inhibitors.[27]

Scheme 4. Mechanistic Studies



Scheme 5. Proposed Catalytic Cycle

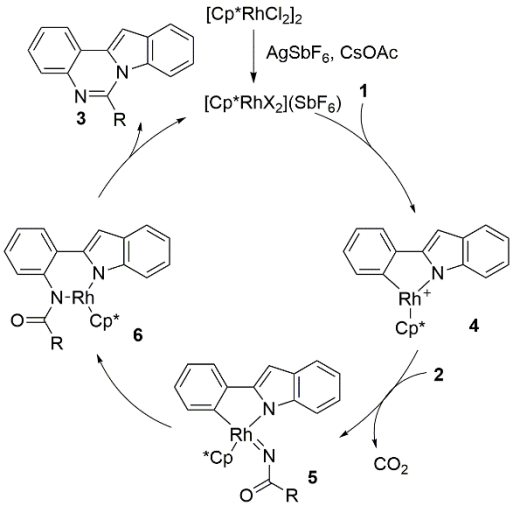


Table 2. Cytotoxicity of 3aa-3ak in Human Cancer Cells[a]

entry	compound	IC50 (μm) PC3	A549	MCF-7
1	**3aa**	229.8	134.9	n/a
2	**3pa**	88.16	63.1	n/a
3	**3ad**	132.2	51.4	252
4	**3ag**	242.8	30.7	n/a
5	**3ak**	158.4	87.4	287.9
6	cisplatin	4.97	12.2	70.4

[a]Selected results are shown. See SI for full details.

In summary, we have reported Rh-catalyzed synthesis of indolo[1,2-c]quinazolines through direct C–H amidation and intramolecular N–H/N–C(O) cyclization of broadly available 2-aryl-1*H*-indoles with dioxazolones. This mild and highly efficient process permits the most straightforward platform for the synthesis of indolo[1,2-c]quinazolines developed to date. The reaction showed broad scope with respect to indole and dioxazolone. The reaction proceeds with high atom economy with H_2O and CO_2 formed as by-products and avoids any substrate pre-functionalization. The potential of this method has been highlighted by the discovery of indolo[1,2-c]quinazolines that exhibit promising antitumor activity. Further studies on the formation of amides via C–H functionalization as well as tandem annulation are underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

J.Z. thanks the China Scholarship Council (No. 201808610096). Financial support was provided by the Foundation for Young Scholars of Shaanxi University of Science and Technology (No. BJ12-26). M.S. thanks Rutgers University and the NSF (CAREER CHE-1650766).

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