Chinese Chemical Letters 31 (2020) 3237–3240

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Communication

Cp*Co(III)-catalyzed C—H amidation of azines with dioxazolones

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ARTICLE INFO

Article history:
Received 3 July 2020
Received in revised form 6 August 2020
Accepted 26 August 2020
Available online 30 August 2020

Keywords:
Cp*Co(III)-catalyzed
Azines
Amidation
Dioxazolone

ABSTRACT

Cp*Co(III)-catalyzed direct C—H amidation of azines has been developed. This conversion could proceed smoothly in the absence of external oxidants, acids or bases, with excellent regioselectivity and broad functional group tolerance. CO_2 was released as the sole byproduct, thus providing an environmentally benign amidation process. The products obtained are important intermediates in organic synthesis.

Nitrogen-containing compounds are widely existed in many natural products, pharmaceutics, and functional materials [1,2]. So far, the main methods for the construction of the C—N bond have been represented by Ullmann and Buchwald–Hartwig amination, using copper or palladium as catalyst [3–6]. Despite the fact that these means are well developed and widely applied, aryl halides or complex ligands are required in most cases. Recently, the direct C—H amination of the aromatic ring and the redox amine source has been developed. The common redox amine sources [7–9], include imidoiodine [10,11], organic azide [12–21], hydroxamate [22–24], heterocyclic amines [25–33]. Among which, dioxazolones are used as effective amidation reagents to construct C—N bonds due to their high efficiency, safety, and ease of preparation [28,33,34].

Azine is an important nitrogen-containing compound, which is widely used in pesticides, medicine, functional materials and other fields [35–40]. Nowadays, direct C—H bond functionalization has been established to build various azine derivatives. Rh(III)-catalyzed *ortho*-alkenylation [41], *ortho*-thioetherification and *ortho*-allylation [42,43], *ortho*-alkylation [44] of azines have been respectively developed by Huang, Zhu and our group (Scheme 1, i–v). Bhanage's group [45] utilized a relatively inexpensive cobalt as a catalyst to achieve the cyclization reaction of azines with two molecules of alkyne through N—N bond cleavage, to synthesize a series of polysubstituted isoquinolines (Scheme 1, i). Subsequently, Shi [46] first developed rhodium-catalyzed *ortho*-C—H sulfamidation of azines and obtained the corresponding sulfamidated products with high regioselectivity. Nevertheless, equivalent oxidant was required (Scheme 1, v). Based on the relevant reports [47–52] and the importance of azines, cobalt-catalyzed directed C—H amidation of azines should be attractive and feasible. In continuation of our ongoing exploration of redox C—H amidation [26,30,53], herein, we report Co-catalyzed amidation of azines with dioxazolones *via* direct C—H activation. This transformation could be carried out smoothly without additional oxidant, acid or base. And, CO_2 is released as the sole byproduct, thus providing an environmentally benign amidation process.

First, we investigated the direct C—H amination with acetophenazine **1a** and dioxazolone **2a** as the model substrates (Table 1). In an initial set of experiment, the expected *ortho*-amided product **3a** was obtained in 25% isolated yield in the presence of [Cp*Co(CO)I_2] (10 mol%), $AgSbF_6$ (20 mol%), and $Cu(OAc)_2$ (20 mol%) in DCE at 80 °C for 12 h (entry 1). Due to the solubility of the substrates, we initiated our studies by examining the effects of the solvent. And DCM was found to be optimal (entries 1—7). The yield was almost unaffected under air, N_2, O_2, respectively. So we decided to conduct the reaction at air atmosphere (entry 8). Considering the redox property of dioxazolone, we tried to avoid the use of $Cu(OAc)_2$ as oxidant. Surprisingly, the yield was increased from 55% to 72% (entry 9). Afterward, the effect of silver salt was investigated (such as $AgSbF_6$, $AgNTf_2$, $AgBF_4$, AgOAc) (entries 9–12), and $AgSbF_6$ gave the better result. However, the corresponding product was not obtained when the silver salt was replaced with KPF_6 (entry 13). Subsequently, some additives were screened (entries 14–18), and yield was slightly reduced compared to the yield in the absence of any additives. It was noting that the desired product **3a** could be obtained in 84% yield when the reaction time was decreased to 8 h because the formation of di-substituted amination as by-product **3aa** was reduced (entry

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https://doi.org/10.1016/j.cclet.2020.08.046
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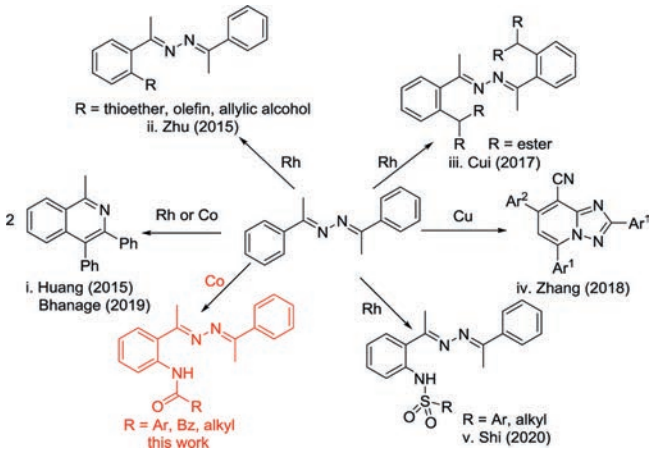
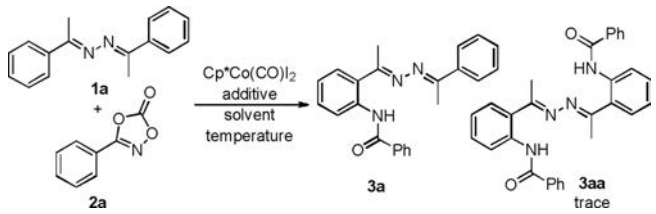


Scheme 1. Direct functionalization of azines by transition metal catalysis.

Table 1
Optimization of direct amidation conditions.[a]



Entry	Ag^+	Additives	Solvent	**3a** Yield (%)[b]
1	$AgSbF_6$	$Cu(OAc)_2$	DCE	25
2	$AgSbF_6$	$Cu(OAc)_2$	Toluene	29
3	$AgSbF_6$	$Cu(OAc)_2$	MeOH	trace
4	$AgSbF_6$	$Cu(OAc)_2$	THF	10
5	$AgSbF_6$	$Cu(OAc)_2$	TFE	16
6	$AgSbF_6$	$Cu(OAc)_2$	HFIP	17
7	$AgSbF_6$	$Cu(OAc)_2$	DCM	55
8	$AgSbF_6$	$Cu(OAc)_2$	DCM	56 [c/d]
9	$AgSbF_6$	–	DCM	72
10	$AgNTf_2$	–	DCM	67
11	$AgBF_4$	–	DCM	Trace
12	AgOAc	–	DCM	Trace
13	KPF_6	–	DCM	Trace
14	$AgSbF_6$	PivOH	DCM	38
15	$AgSbF_6$	NaOAc	DCM	47
16	$AgSbF_6$	KOAc	DCM	61
17	$AgSbF_6$	CsOAc	DCM	14
18	$AgSbF_6$	NaOPiv·H_2O	DCM	57
19[e]	$AgSbF_6$	–	DCM	84
20[e,f]	$AgSbF_6$	–	DCM	54

DCE: 1,2-dichloroethane; THF: Tetrahydrofuran; TFE: 2,2,2-trifluoroethanol; HFIP: hexafluoro isopropanol; DCM: 1,2-dichloromethane.

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Cp*Co(CO)I_2] (10 mol%), Ag^+ (20 mol%), additives (20 mol%), solvent (1 mL), 12 h, under air, 100 °C, sealed.

[b] Isolated yields.

[c] O_2.

[d] N_2.

[e] 8 h.

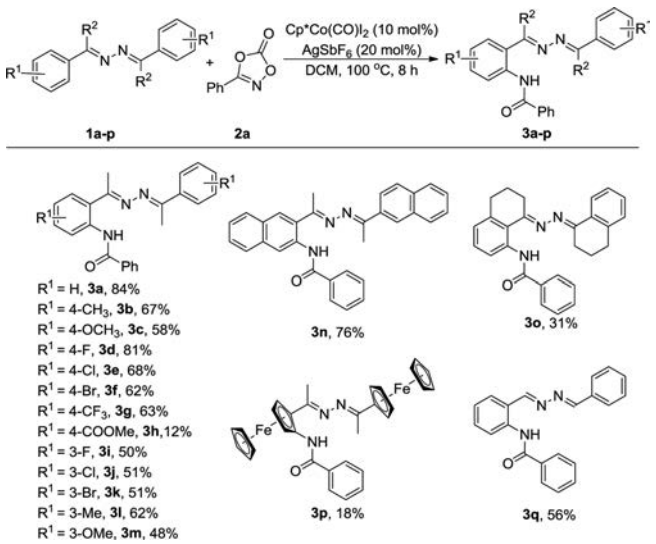
[f] [Cp*Co(CO)I_2] (5 mol%), $AgSbF_6$ (10 mol%).

19). Reducing the amount of catalyst to 5 mol%, only 54% of product **3a** was obtained (entry 20). Finally, the optimal reaction conditions were determined as follows: [Cp*Co(CO)I_2] (10 mol%), $AgSbF_6$ (20 mol%), in 1 mL DCM under air atmosphere at 100 °C for 8 h.

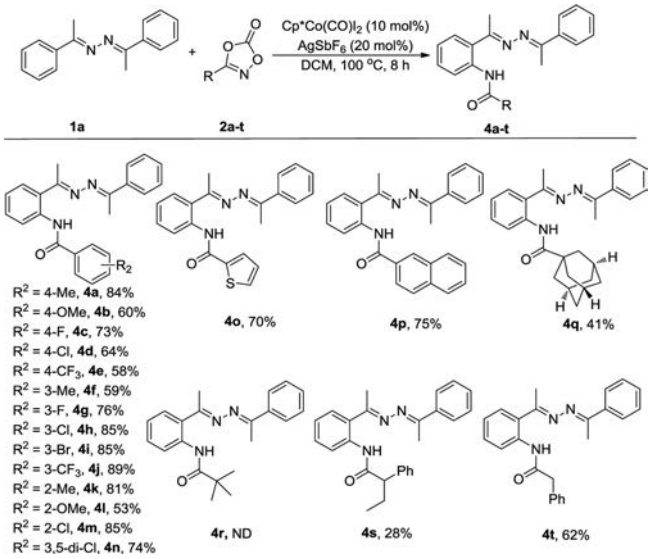
With the optimized conditions in hand, the scope of azines was next examined (Scheme 2). The coupling of dioxazolone (**2a**) and *para*-substituted azines **1b**–**1c** with electron-donating groups (-Me and -OMe) was found to react smoothly more than *para*-substituted azines **1h** with electron withdrawing groups (COOMe). The 4-halo azines (**1d**-**1g**) reacted with the dioxazolone to give the target products in moderate to good yields, significantly better than 3-halo azines (**1i**-**1k**). For the same substituent, the overall yields of 4-substituted products (**3b**-**3f**, 58%–81%) were significantly higher than that of 3-substituted products (**3i**-**3m**, 48%–62%). The reaction of **1p** was sluggish and only 18% product **3p** was obtained. Surprisingly, **3n** was afforded in 76% yield with good regioselectivity. In a similar fashion, 1,2-bis((*E*)-3,4-dihydronaphthalen-1(2*H*)-ylidene) hydrazine **1o** and bis(ferrocenyl acetone) hydrazine **1p** were also tolerated. Moreover, dibenzaldehyde hydrazine provided the amidated product **3q** in 56% yield.

To further examine the substrate scope of this procedure, a series of dioxazolones (**2a**-**2t**) were screened for coupling with acetophenazine **1a** (Scheme 3). Both electron-donating (*e.g.*, Me, MeO) and electron-withdrawing groups (*e.g.*, F, Cl, Br, CF_3, 3,5-di-Cl) in benzene were compatible with this reaction protocol. Dioxazolones bearing electron-withdrawing substituents on the aromatic ring were generally more efficient, giving the desired amidated product in relatively higher yields. Importantly, halides, such as chloride (**4d**, **4h**, **4m** and **4n**), bromide (**4i**), could survive under the optimized conditions, giving the desired products in 58%–85% yields. Furthermore, thiophene- and naphthalene-functionalized dioxazolones also reacted smoothly to afford products **4o** and **4p** in 70% and 75% yields, respectively. Nevertheless, aliphatic dioxazolone, such as **2r**, was not amenable to this protocol. The yield of the corresponding products (**4t**, 62%; **4q**, 41%; **4s**, 28%) decreased along with increasing the steric hindrance for aliphatic-dioxazolone (**2t**, **2q**, **2s**).

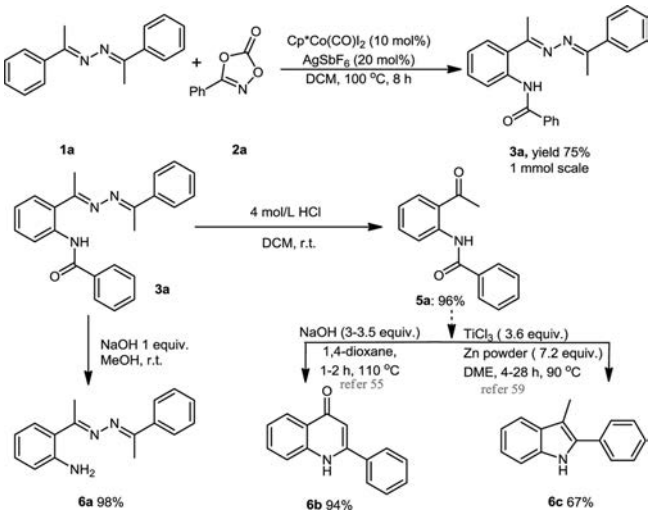
To demonstrate the practical application of the amidation reaction, a scaling up experiment was carried out with 1 mmol scale of acetophenazine **1a**, which successfully afforded the aminated product **3a** in 75% under the optimal reaction conditions (Scheme 4). The product **3a** could be hydrolyzed, treated by 1 equiv. of sodium hydroxide in methanol, to obtain **6a** in 98% yield. Similarly, **3a** was stirred in 4 mol/L hydrochloric acid solution in DCM at room temperature to give the hydrolysis product **5a** in 96% yield. According to the literature, **5a** could be easily transformed to the corresponding biologically active 2-phenyl-4-quinolinone (**6b**) [54–57] and 3-methyl-2-phenylindole (**6c**) [58–60].



Scheme 2. Scope of azines. Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Cp*Co(CO)I_2] (10 mol%), $AgSbF_6$ (20 mol%), DCM (1 mL), 8 h, 100 °C, sealed. Isolated yields.



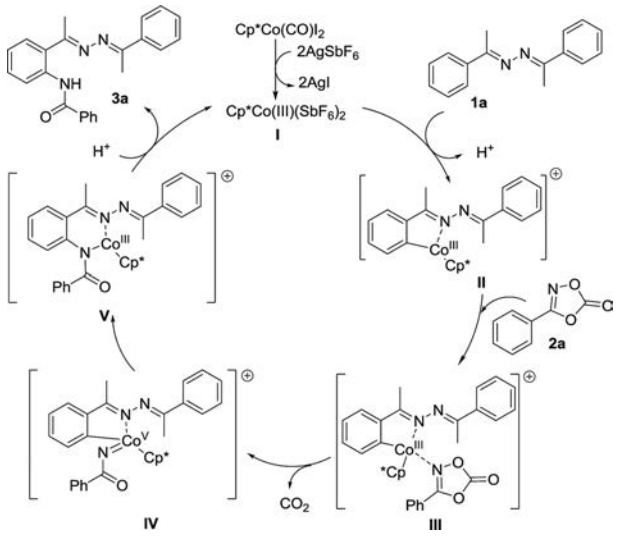
Scheme 3. Scope of dioxazolones. Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), [Cp*Co(CO)I_2] (10 mol%), $AgSbF_6$ (20 mol%), DCM (1 mL), 8 h, under air, 100 °C, sealed. Isolated yields.



Scheme 4. Scale-up experiment and transformations of the amidated product.

Based on the above results and previous reports [61,62], a plausible reaction mechanism was proposed (Scheme 5). Firstly, the reactive cationic Cp^*Co^{III} species **I** was generated with the assistance of $AgSbF_6$. Subsequently, Cp^*Co^{III} species **I** coordinated to nitrogen atom of the substrate **1a**, and formed cobaltacycle **II** through C—H bond cleavage. Cobaltacycle **II** subsequently coordinated with nitrogen atom of **2a** to form intermediate **III**. Next, nitrogen carbine intermediate **IV** was afforded by extrusion of CO_2 as a single byproduct. Subsequently, migratory insertion of intermediate **IV** provided the intermediate **V**. Finally, proton-demetallization of intermediate **V** liberated the desired product **3a** along with the regeneration of the active catalyst into the next cycle.

In summary, we have developed an efficient and convenient cobalt(III)-catalyzed C—H amidation of azines with dioxazolones. The method could be scalable and compatible with a broad range of functional groups. The results have paved the way toward construction of 2-phenyl-4-quinolinone and 3-methyl-2-phenyl-indole derivatives, which exist in drug molecule with broad



Scheme 5. Proposed reaction mechanism.

anti-infection, anti-tumor, anti-inflammatory and other biological activities.

Declaration of competing interest

No conflict of interest exits in the submission of this manuscript, and manuscript is approved by all authors.

Acknowledgments

This work was financially supported by the Ministry of Science and Technology of China (No. 2016YFE0132600), Henan Center for Outstanding Overseas Scientists (No. GZS2020001).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.08.046.

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