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Cobalt-Catalyzed *Ortho*-C(sp^2)−H Amidation of Benzaldehydes with Dioxazolones Using Transient Directing Groups

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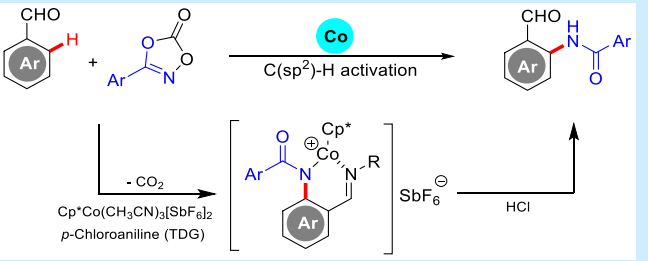
Supporting Information

ABSTRACT: An efficient and convenient cobalt-catalyzed *ortho*-C(sp^2)−H amidation of benzaldehydes employing dioxazolones as the aminating reagent has been developed. The key feature of this protocol is the use of green and economic earth-abundant metals cobalt as the catalyst with the *p*-chloroaniline as the transient directing group. Further application of our approach was demonstrated by the synthesis of C1r serine protease inhibitor **45** and elastase inhibitor **49**.



The highly efficient C−N bond formation has been a focus of synthetic chemistry because nitrogen-containing molecules are very important and widely present in pharmaceutical agents, natural products, and synthetic intermediates.[1] Among these extensively explored C−N bond-forming methods, the direct and high selective conversion of an unactivated C−H bond to the corresponding C−N bond has emerged as an ideal and attractive strategy with great atom and step economy.

o-Aminobenzaldehyde and its derivatives can be used to construct plentiful skeletons of biologically active molecules (Figure 1)[2] and organic materials; thus, the development of new C−H amination procedures for the synthesis of 2-aminobenzaldehydes has attracted a lot of attention in recent years. In the past decade, transition-metal-catalyzed, directing group mediated intermolecular regioselectivity C(sp^2)−H amination of arenes has been well documented.[3] However, the aldehyde-assisted *ortho*-C−H amination is relatively rare,[4] which poses a major challenge regarding its relatively weak coordination ability and the instability of the aldehyde group.[5]

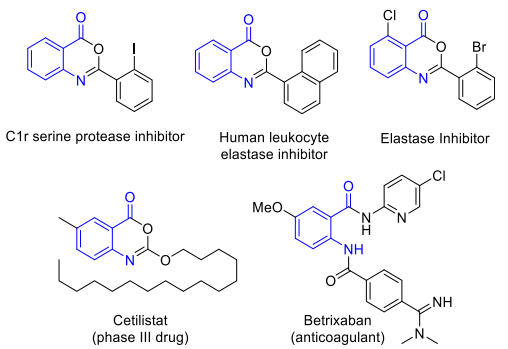
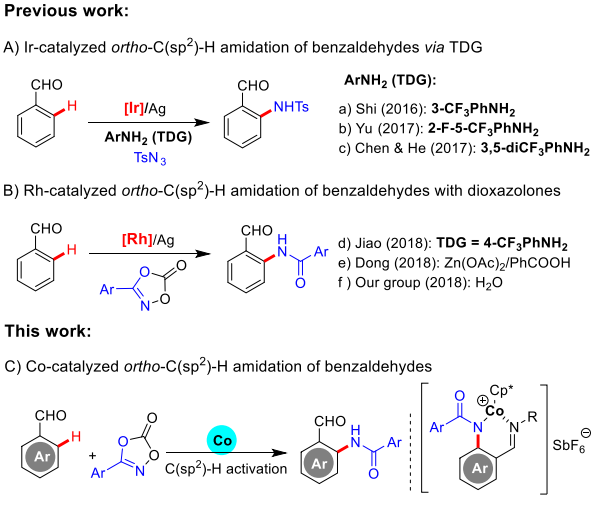


Figure 1. Skeletons of some bioactive 2-formylaniline.

To overcome this deficiency, Shi,[6a] Yu,[6b] and Chen and He[6c] independently developed more direct and efficient Ir-catalyzed *ortho*-C−H amidations of benzaldehydes employing substituted anilines as transient directing groups (TDGs) with TsN_3 as the aminating reagent (Scheme 1A). In 2018, Jiao[7a] described the Rh-catalyzed *ortho*-C−H amidations of benzaldehydes with dioxazolones using *p*-trifluoromethylaniline (**T3**)

Scheme 1. Transition-Metal-Catalyzed *Ortho*-C−H Amination of Benzaldehydes



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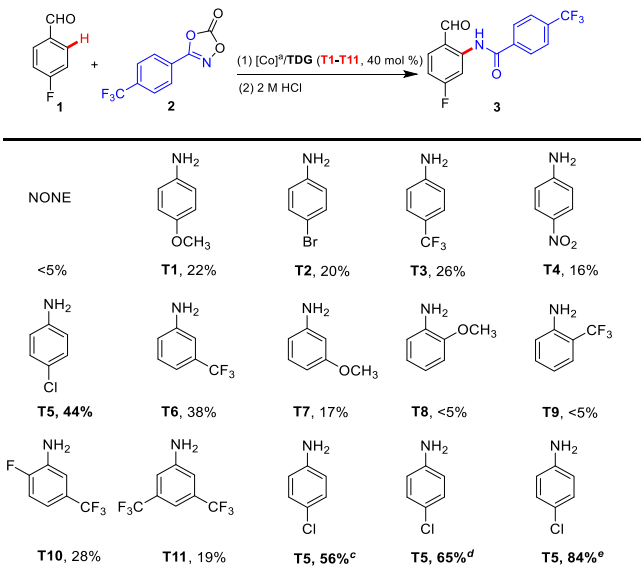
as TDG. Dong[7b] reported Rh-catalyzed direct *ortho*-C(sp^2)−H amidation of benzaldehydes with additives of $Zn(OAc)_2 \cdot 2H_2O$/PhCOOH. Zhang[7c] reported an efficient Rh-catalyzed *ortho*-C−H amidation method employing H_2O as the key promoter, and the detailed mechanistic studies indicated that the catalyst precursor interacted with dioxazolones and H_2O to generate the active catalytic species (Scheme 1B).

Although the precious metal catalysts Rh and Ir have been successfully used for the direct *ortho*-C−H amination of benzaldehyde via the TDG strategy, their high cost and toxicity limit their application and potential pharmaceutical chemical studies;[8] to date, using inexpensive or earth-abundant metals as catalysts in this protocol has not been reported. In our ongoing efforts to develop effective inexpensive metal-catalyzed C−H activation and amination methods,[9] in this paper, we report the first Co-catalyzed direct *ortho*-C(sp^2)−H amidation of benzaldehydes using dioxazolones as the aminating source with *p*-chloroaniline as the TDG. This protocol provides a green and convenient strategy for the efficient synthesis of diversely functionalized *ortho*-aminobenzaldehydes. Further applications were demonstrated by the successful synthesis of C1r serine protease inhibitor (**45**) and elastase inhibitor (**49**)[10]

We have carried out our investigation employing 4-fluorobenzaldehyde **1** and dioxazolone[11] **2** in the presence of 10 mol % of $Cp^*Co(CH_3CN)_3[SbF_6]_2$ (***Cat.* A**) in DCE under argon for 12 h. After an initial screening of the reaction conditions, we found that a TDG was essential for the C−H amidation, and just a trace desired product **3** was detected in the absence of arylamine (see the Supporting Information). Thus, we further screened a series of arylamines as TDG additives to test this C−H amidation reaction (Table 1). Interestingly, the previously reported TDGs in precious metal Rh (**T10** and **T11**) and Ir (**T3**) catalytic systems were not suitable for our cobalt-catalyzed C−H amidation catalytic system. To our delight, *p*-chloroaniline (**T5**) was found to be the most effective TDG to afford the amidation product **3** in 44% isolated yield (**T5**). Although the product **3** was obtained in 38% yield using *m*-trifluoromethylaniline as TDG (**T6**), the cheaper *p*-chloroaniline (**T5**) motivated us to use it as the transient directing group in these Co-catalyzed C−H amidation reactions. After varying the loading amounts of *p*-chloroaniline (**T5**), we found that an 84% isolated yield of desired products **3** was obtained under the optimized reaction conditions: 10 mol % of $Cp^*Co(CH_3CN)_3[SbF_6]_2$ (***Cat.* A**) and 1.0 equiv of *p*-chloroaniline (**T5**) in DCE at 120 °C under Ar for 6 h.

Table 1. Evaluation of Aniline Promoters[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), ***Cat.* A** (10 mol %), and TDG (0.4 equiv) in DCE (1 mL) at 120 °C under Ar for 12 h. [b]Isolated yield. [c]0.6 equiv of *p*-chloroaniline. [d]0.8 equiv of *p*-chloroaniline. [e]1.0 equiv of *p*-chloroaniline for 6 h.

After establishing the optimized conditions, we probed the scope of benzaldehydes with dioxazolone **2** (Table 2). A wide range of benzaldehydes were well-tolerated in our Co-catalyzed system and gave the *ortho*-amidated benzaldehydes in good to excellent yields. Subsequently, the *ortho*-, *meta*-, and *para*-substituted benzaldehyde substrates (Table 2A−C) were used to examine the effects of sterics hindrance and electrons on the benzenes. The results indicate that the benzaldehydes with halogen substitution and electron-donating groups (alkyl, OMe, etc.) were found to be well-tolerated and gave the amidation products in good to excellent yields. Comparatively, the benzaldehydes with the strong electron-withdrawing groups (CN, NO_2, etc.) notably reduce the reactivity of C−H amidations. Moreover, when the *meta*-substituted benzaldehydes (Table 2B) demonstrated high regioselectivity, less hindered *ortho*-C−H was activated and the sole regioisomers **11**−**15** were obtained. In addition, this process shows high monoselectivity, and the monoamidated products **17**−**25** were obtained in 46−81% isolated yield. No diamidated products were observed in the reaction system (Table 2C). Multi-substituted benzaldehydes also gave the desired C−H amidation product **27**−**35** in good to excellent yields (Table 2D), and the high regioselectivity was confirmed by X-ray crystallographic analysis of compound **34**. Furthermore, we investigated the generality of dioxazolones. The results showed that the aryl dioxazolones both with electron-donating and electron-withdrawing substituents on the phenyl ring reacted smoothly to give the corresponding amidated products **36**−**41** in good yields (Table 2E).

To elucidate the reaction mechanism, a series of preliminary deuteration experiments were carried. The kinetic isotope effect (KIE) was determined to be 2.15, which indicated that the C−H activation might be the rate-limiting step. The radical capture experiments suggested that the radical mechanism was unlikely to be involved in our reaction (see the Supporting Information).

On the basis of the results and previous reported studies,[7,11b,d,12] a possible mechanism was proposed (Scheme 2). Initially, condensation between **42** and arylamine generates imine **A**. Subsequently, the combination of Co catalyst with imine undergoes C−H bond activation via an acetate-assisted intramolecular C−H concerted metalation−deprotonation (CMD) to generate intermediate **II**. Next, coordination of the dioxazolones **B** forms the intermediate **III**, which undergoes the intermolecular migration insertion to afford intermediate **IV** with the extrusion of CO_2. Finally, the protonation of intermediate **IV** by formed $HSbF_6$ regenerates the Co catalysts **I** and **C**.

To demonstrate the application of our earth-abundant metal Co-catalyzed C−H amidation method as an efficient and versatile synthetic strategy, two active molecules C1r serine protease inhibitor **45**[10a] and elastase Inhibitor **49**[10b] were synthesized under our mild conditions with good yield, which

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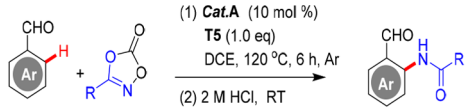
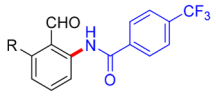
Table 2. Substrate Scope of Benzaldehydes[a,b]

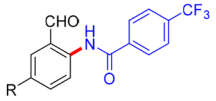


A) *ortho*-substituted benzaldehydes

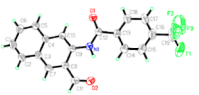


4, R = F, 72%
5, R = Cl, 80%
6, R = Br, 78%
7, R = I, 76%
8, R = CH_3, 81%
9, R = OCH_3, 78%
10, R = CF_3, 9%

B) *meta*-substituted benzaldehydes



11, R = Cl, 43%
12, R = Br, 41%
13, R = I, 48%
14, R = CH_3, 63%
15, R = OCH_3, 28%
16, R = CF_3, NR[c]



X-Ray of **34**
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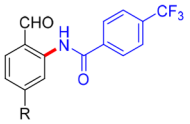
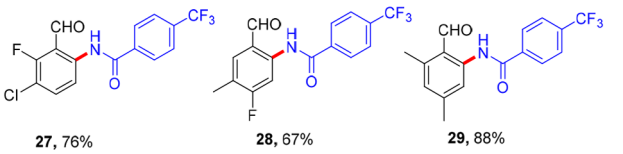
C) *para*-substituted benzaldehydes

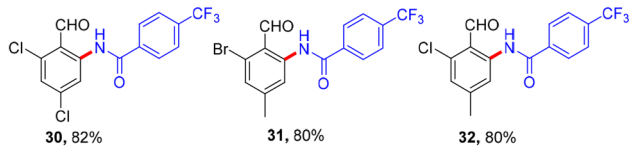


17, R = Cl, 80%
18, R = Br, 81%
19, R = I, 75%
20, R = CH_3, 74%
21, R = OCH_3, 60%
22, R = SCH_3, 81%
23, R = Et, 77%
24, R = Ph, 53%
25, R = *t*Bu, 46%
26, R = CF_3, NR

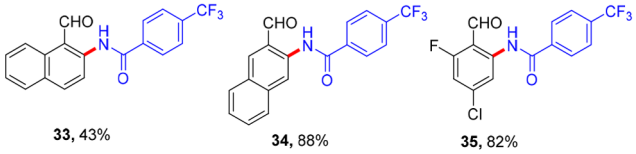
D) *multi*-substituted benzaldehydes



27, 76%
28, 67%
29, 88%

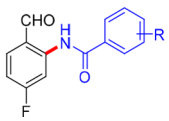


30, 82%
31, 80%
32, 80%



33, 43%
34, 88%
35, 82%

E) substituted dioxazolones



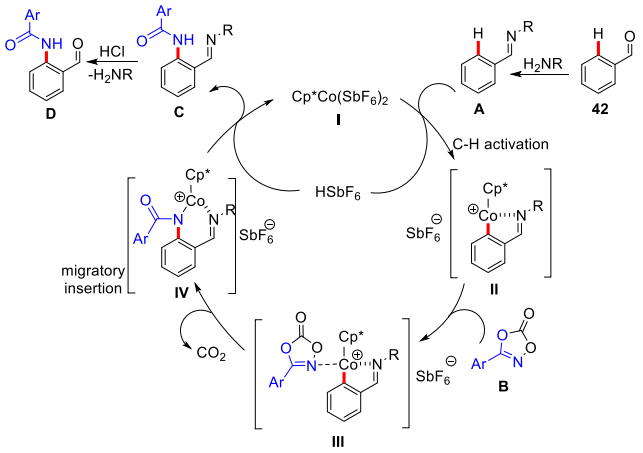
36, R = 2-CH_3, 78%
37, R = 3-CH_3, 75%
38, R = 3-CF_3, 67%
39, R = 4-CH_3, 71%
40, R = 4-Cl, 68%
41, R = 4-OMe, 78%

[a]Reaction conditions: benzaldehyde (0.2 mmol), dioxazolone (0.4 mmol), ***Cat.* A** (10 mol %), and **T5** (0.2 mmol) in DCE (1 mL) at 120 °C under Ar for 6 h. [b]Isolated yield. [c]NR = no reaction.

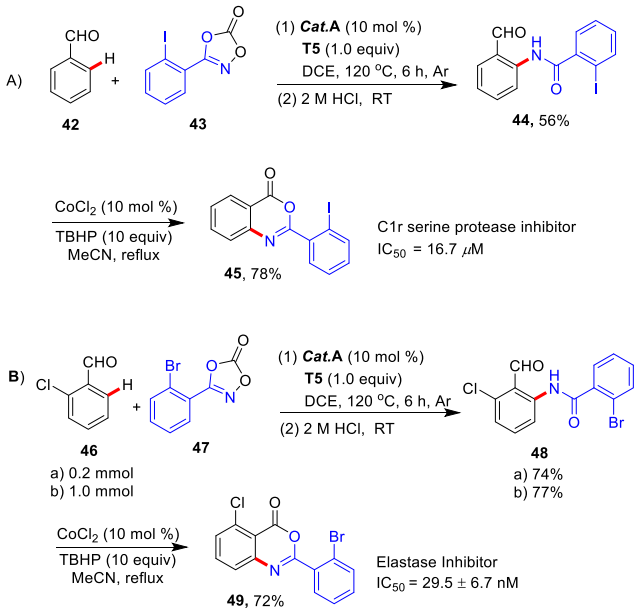
provides a more efficient synthetic route for the synthesis of drug molecules and constructs scaffolds with bioactive molecules (Scheme 3).

In summary, we have developed the first direct and convenient Co-catalyzed *ortho*-C−H amidation of benzaldehydes using *p*-chloroaniline as the transient directing group. These reactions are operationally simple and robust, and the cobalt catalyst system avoids the use of expensive noble metals Rh and Ir. In addition, the reaction produced broad and structurally diverse *ortho*-amidated benzaldehydes in good to high yield. The practicality of our approach was demonstrated

Scheme 2. Proposed Mechanism



Scheme 3. Synthetic Applicability



by the synthesis of C1r serine protease inhibitor **45** and elastase Inhibitor **49**. Further applications of this C−H amidation methodology in the synthesis of complex products are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02632.

Experimental procedures, analytical data of products, and copies of ^{1}H and ^{13}C spectra (PDF)

Accession Codes

CCDC 1940485 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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