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ONE-STEP SYNTHESIS OF 4*H*-3,1-BENZOXAZIN-4-ONES FROM WEINREB AMIDES AND 1,4,2-DIOXAZOL-5-ONES VIA COBALT-CATALYZED C–H BOND ACTIVATION

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Dedicated to Professor Tohru Fukuyama on the occasion of his 70th birthday

Abstract – A one-step synthesis of 4*H*-3,1-benzoxazin-4-ones from readily available Weinreb amides and 1,4,2-dioxazol-5-ones under Cp*Co(III) catalysis is described. The reactions proceeded in moderate to good yields with high functional group compatibility.

4*H*-3,1-Benzoxazin-4-ones (benzoxazinones, **1**)[1] inhibit a variety of proteases, such as chymotrypsin,[2a] HL elastase,[2b,c] HSV-1 protease,[2d] cathepsin G,[2e] C1r,[2f] and human chymase.[2g] Cetilistat, a lipase inhibitor containing a benzoxazinone core, was reported as an anti-obesity agent.[3] In addition, benzoxazinones **1** can be converted to quinazolin-4(3*H*)-ones.[1] The importance of **1** in medicinal chemistry and drug-discovery prompted organic chemists to investigate their synthetic methods (Figure 1).[1,4-7] 2-Aminobenzoic acids and related derivatives are classical and frequently used starting materials for the synthesis of benzoxazinones.[1] Transition metal-catalyzed carbonylation[4] or amination[5] reactions of *ortho*-functionalized aryl halides, oxidation of indoles,[1,6] and oxidation of other appropriate precursors[7] provide **1**. Preparation of these synthetic precursors, however, often requires multiple steps to access functionalized derivatives for investigation of the biological activities (Figure 1a).

On the other hand, transition metal-catalyzed directing group-assisted C–H bond activation[8] enables the synthesis of benzoxazinones **1** from simpler compounds. Pd(II)-catalyzed C–H carbonylation reactions of aniline derivatives using CO gas were reported by Lloyd-Jones, Booker-Milburn, and co-workers;[9a] and Yu and co-workers[9b] (Figure 1b). A major drawback of these methods, however, is the requirement of highly toxic gaseous CO. Cp*Rh/Ir(III)-catalyzed *ortho*-C–H amidation reactions of aromatic aldehydes[10] or their equivalents[11] afforded 2-aminobenzaldehyde derivatives, which were converted to **1** (Figure 1c).

In these cases, an additional oxidation step was necessary as the oxidation state of the directing group differs from that of **1**.

Here we report a one-step synthesis of benzoxazinones **1** from Weinreb amides **2** by directed C–H amidation using 1,4,2-dioxazol-5-ones (dioxazolones, **3**) under Cp*Co(III) catalysis and subsequent cyclization.[12,13] Our protocol conveniently provided **1** using readily available starting materials and catalyst[14] without any additional redox or cyclization step (Figure 1d).

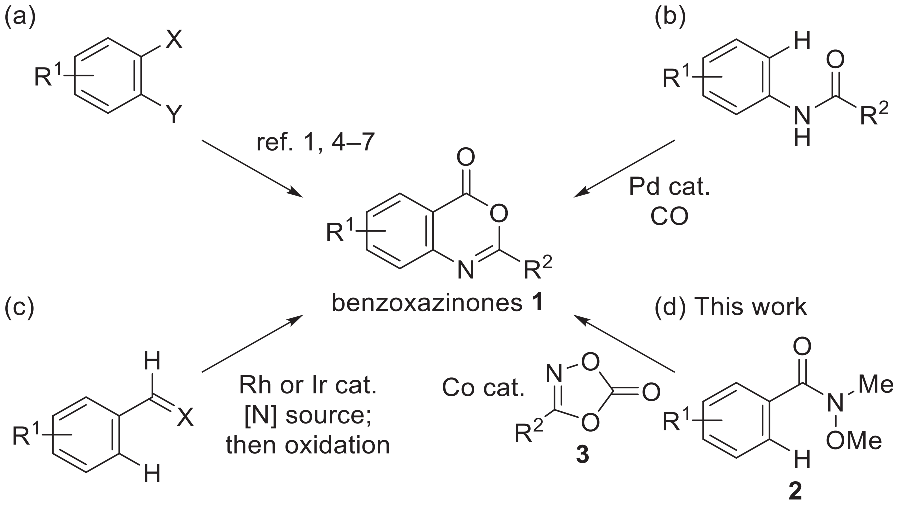
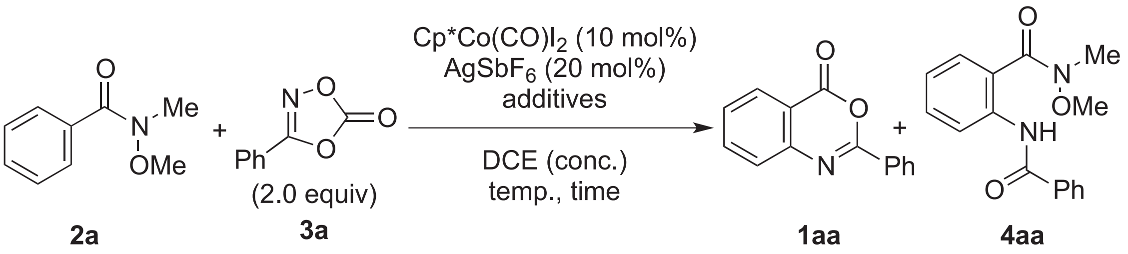


Figure 1. Synthetic methods of benzoxazinones **1**

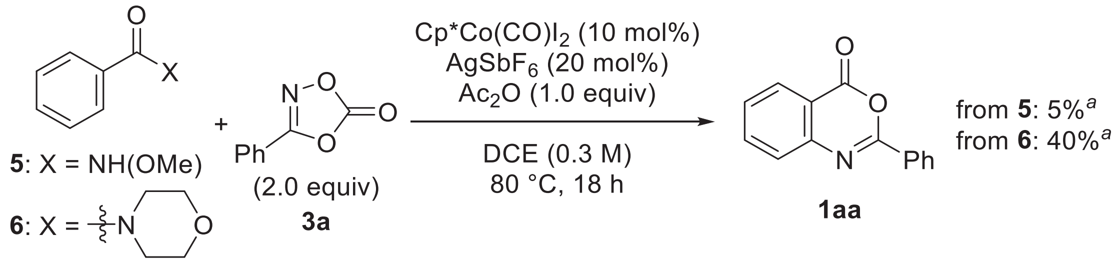
We recently reported Cp*Co(III)-catalyzed C–H amidation of Weinreb amides **2** using dioxazolones **3**[15a,16,17] as a part of our studies on Cp*Co(III) catalysis.[15] While investigating this reaction, we found that benzoxazinone **1aa** was obtained as a major product along with a smaller amount of amidation product **4aa** when **2a** and **3a** were heated at 100 °C for 24 h in DCE with catalytic amounts of $Cp^*Co(CO)I_2$, $AgSbF_6$, and AgOAc (Table 1, entry 1). Benzoxazinone **1aa** would be formed from amidation product **4aa** through nucleophilic attack of the introduced amide to the relatively electrophilic Weinreb amide moiety, releasing *N*,*O*-dimethylhydroxylamine. We next investigated the reaction conditions to maximize the yield of **4aa**. After several investigations, we speculated that the released *N*,*O*-dimethylhydroxylamine would be problematic because it can reversibly react with **1aa** to give **4aa**, and/or coordinate to the cobalt center to inhibit the catalysis. Therefore, we added acetic anhydride to scavenge *N*,*O*-dimethylhydroxylamine, and the yield was improved to 73% (entry 2). In this case, **4aa** was not observed in the crude mixture. Almost the same result was observed when the concentration was increased to 0.3 M (entry 3). A shorter reaction time and lower temperature (entry 4, 80 °C for 18 h) slightly improved the yield, possibly due to the decreased decomposition of **1aa**. Finally, the reaction proceeded smoothly in the absence of AgOAc to provide **1aa** in 84% isolated yield (entry 5). We also examined *O*-methyl hydroxamate **5** and morpholine amide **6** as the substrate (Scheme 1). The reaction using **5** afforded a large amount of unidentified byproducts, and **1aa** was obtained only in 5% yield. Substrate **6** afforded **1aa** as a major product, but the starting material remained in 50% after 18 h, indicating the low reactivity of **6** in the C–H amidation step.

Table 1. Optimization of reaction conditions



entry	additives	conc. (X M)	temp. (°C)	time (h)	% yield[b]	
					1aa	**4aa**
1	AgOAc (10 mol%)	0.1	100	24	44	26
2	AgOAc (10 mol%) Ac_2O (1.0 equiv)	0.1	100	24	73	<5
3	AgOAc (10 mol%) Ac_2O (1.0 equiv)	0.3	100	24	73	<5
4	AgOAc (10 mol%) Ac_2O (1.0 equiv)	0.3	80	18	81	<5
5	Ac_2O (1.0 equiv)	0.3	80	18	86 (84[c])	<5

[a] Reactions were performed using **2a** (0.10 mmol), **3a** (0.20 mmol), $Cp^*Co(CO)I_2$ (0.01 mmol), $AgSbF_6$ (0.02 mmol), and additives in DCE unless otherwise noted. [b] Determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield.



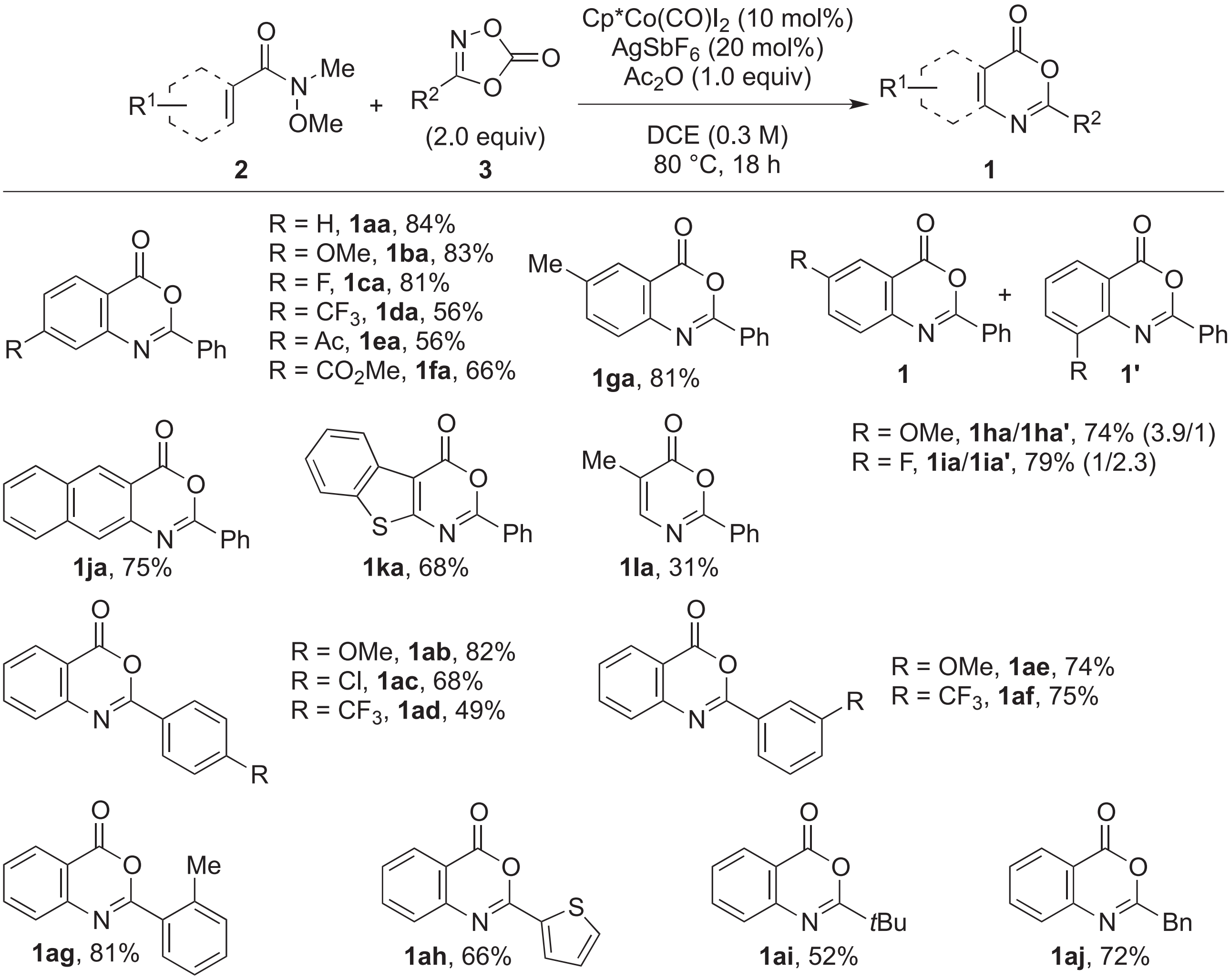
[a] Determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard.

Scheme 1. Reactions using other amides as substrate

The substrate scope of our optimized conditions to give benzoxazinones **1** is summarized in Table 2. Aromatic Weinreb amides bearing various functional groups at the *para*-position afforded **1aa**–**1fa** in 56%–84% yields. While *meta*-Me-substituted Weinreb amide **2g** reacted exclusively at the less hindered

C–H bond to give **1ga**, Weinreb amides with a *meta*-F- and *meta*-OMe-substituent afforded regioisomeric mixtures (**1ha**/**1ha′** and **1ia**/**1ia′**) with moderate selectivities. 2-Naphthyl- and 3-benzothienyl Weinreb amides **2j** and **2k** successfully underwent the reaction to give tricyclic products **1ja** and **1ka**. It is noteworthy that α,β-unsaturated Weinreb amide **2l** provided monocyclic product **1la**, although the yield was diminished. The major product of this reaction is a C–H amidation product **4la** (ca. 50% yield). On the other hand, Weinreb amides derived from acrylic acid and crotonic acid afforded no desired products, and unidentified byproducts were observed in both cases. The presented protocol demonstrated the wide scope of dioxazolones; aromatic, heteroaromatic, and aliphatic dioxazolones were well tolerated and afforded moderate to good yields (**1ab**–**1aj**). Benzoxazinone **1aj** was slightly sensitive to hydrolysis.

Table 2. Substrate scope



[a] Reactions were performed using **2** (0.30 mmol), **3** (0.60 mmol), Cp*Co(CO)I_2 (0.03 mmol), $AgSbF_6$ (0.06 mmol), and Ac_2O (0.30 mmol) in DCE (1 mL). Isolated yields were shown.

A proposed catalytic cycle and reaction mechanism for **1aa** based on previous reports[16] of Cp*Co(III)-catalyzed C–H amidation reactions is shown in Figure 2. Iodide abstraction from [Cp*Co(CO)I_2] with $AgSbF_6$ generates cationic species **I**, which undergoes coordination of **2a** (**II**) and C–H bond activation to give metallacycle **III**. After coordination of dioxazolone **3a** to form **IV**, CO_2 extrusion and insertion of the nitrogen to the C–Co bond generate **V**. Proto-demetallation of **V** regenerates the catalyst with the release of intermediate **4aa**. Cyclization of **4aa** provides benzoxazinone **1aa** and *N*,*O*-dimethylhydroxylamine. The final cyclization step would be reversible, and **1aa** and **4aa** would be in equilibrium. When we treated **1aa** with *N*,*O*-dimethylhydroxylamine hydrochloride and K_2CO_3 in DCE at 80 °C for 3 h, the 53:47 mixture of **1aa** and **4aa** was obtained (Scheme 2). This result proved the reversibility of the cyclization, and indicated that the equilibrium constant is not sufficient. Therefore, benzoxazinone **1aa** was obtained as a sole product by trapping *N*,*O*-dimethylhydroxylamine with Ac_2O. We detected **7** by ^{1}H NMR analysis of the crude reaction mixture.

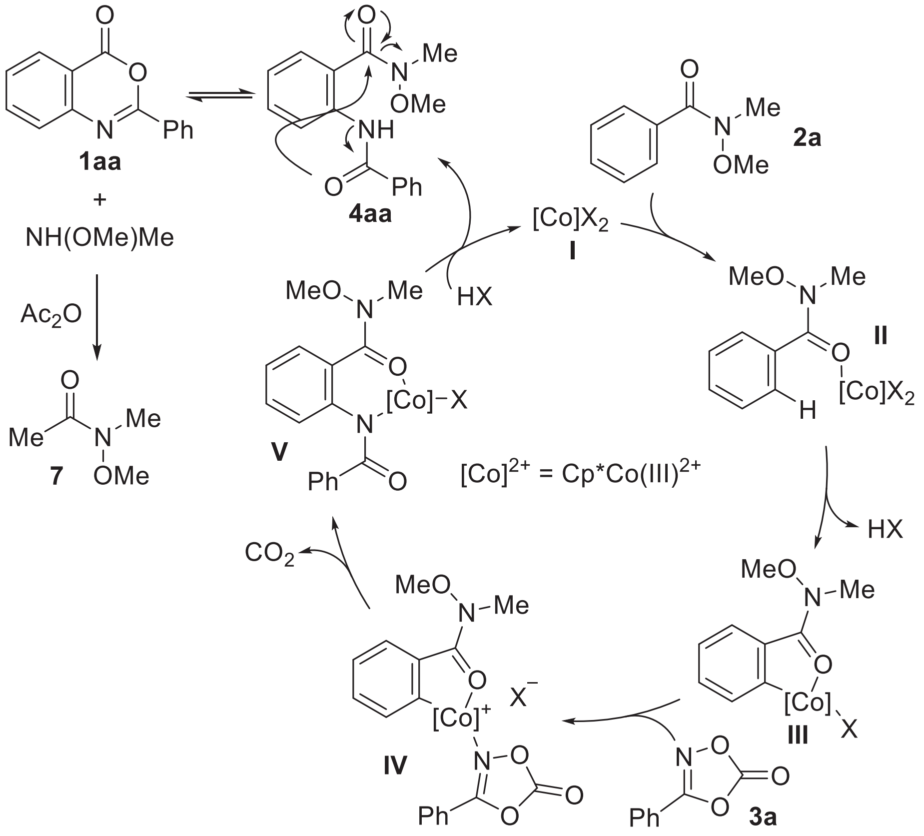
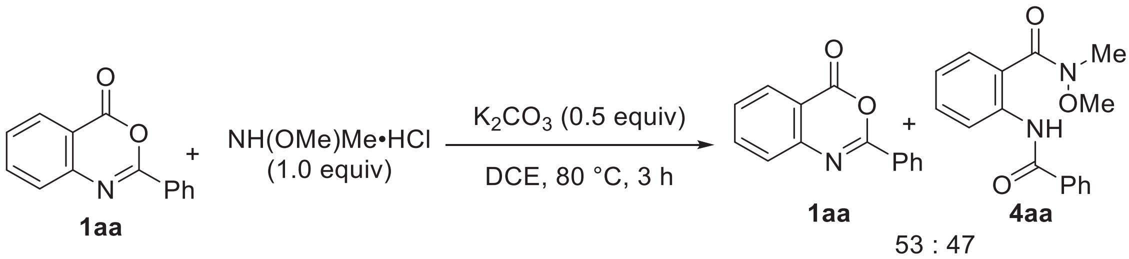


Figure 2. Proposed catalytic cycle and reaction mechanism



Scheme 2. Reversible reaction of **1aa** and *N,O*-dimethylhydroxylamine

In summary, we demonstrated that benzoxazinones **1** were obtained in only one step from Weinreb amides **2** and dioxazolones **3** with high functional group compatibility under Cp*Co(III) catalysis. The presented method may enable fast and easy access to functionalized benzoxazinones **1** for the discovery of new biologically active derivatives.

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SUPPORTING INFORMATION

Supplementary (synthesis of the starting azides, HPLC chromatograms, IR, 1H and 13C NMR, MS spectra, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/25790/99/1.

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