OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Cobalt-Catalyzed Direct Carbonylative Synthesis of Free (*NH*)-Benzo[*cd*]indol-2(1*H*)-ones from Naphthylamides

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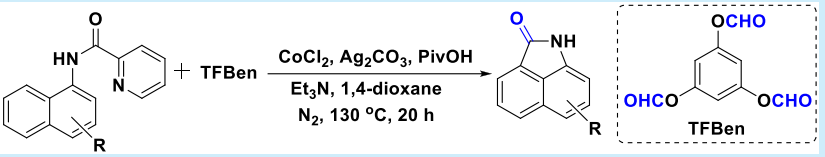
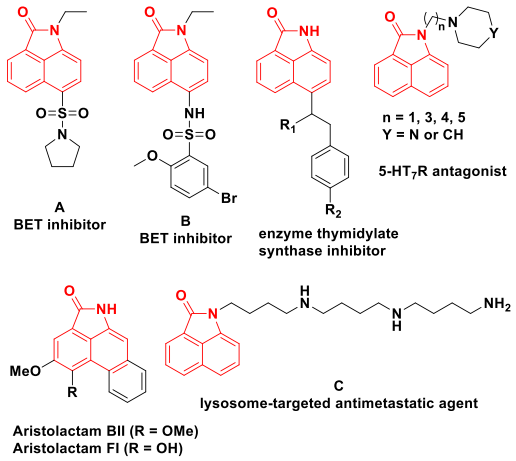
Supporting Information



ABSTRACT: A cobalt-catalyzed C−H carbonylation of naphthylamides for the synthesis of benzo[*cd*]indol-2(1*H*)-one scaffolds has been developed. The reaction employs a traceless directing group and uses benzene-1,3,5-triyl triormate as the CO source, affording various free (*NH*)-benzo[*cd*]indol-2(1*H*)-ones in moderate to high yields (up to 88%). Using this protocol, the total synthesis of BET bromodomain inhibitors A and B was accomplished as well.

Benzo[*cd*]indol-2(1*H*)-ones are frequently found as a significant scaffold in a wide range of pharmaceuticals, dyes, natural products, and biologically active compounds.[1−5] For example, as shown in Scheme 1, compounds A and B represent a new and potent class of BET bromodomain inhibitors exhibiting antitumor and anti-inflammatory activities.[1] Compound **C** is a lysosome-targeted agent with dual bioimaging and antimetastatic features in cancer therapy.[2] Aristolactams, naturally occurring phenanthrene lactam alkaloids, have been used as folk medicines with various biological activities (Scheme 1).[3a]

Scheme 1. Selected Pharmaceuticals and Natural Products of Benzo[*Cd*]indol-2(1*H*)-ones



Due to the extraordinary structure of benzo[*cd*]indol-2(1*H*)-ones, only a few synthetic approaches have been realized for their synthesis. Traditionally, benzo[*cd*]indol-2(1*H*)-ones are prepared from the reaction of 1,8-naphthalic anhydride with hydroxylammonium chloride.[1a,5f,6] However, this reaction is limited to a very narrow substrate scope. On the other hand, transition-metal-catalyzed carbonylative transformation of a C−H bond is a powerful tool in the construction of carbonyl-containing compounds.[7,8] In 2016, Lei and co-workers reported a novel $PdCl_2$ (10 mol %) and $Cu(OAc)_2$ (30 mol %) co-catalyzed aerobic C−H bond activation/*N*-dealkylative carbonylation of naphthylamines to access benzo[*cd*]indol-2(1*H*)-ones.[9] It is noted that C−H bond activation occurs selectively at the C8 position of the naphthylamines in this reaction. Under a carbon monoxide and oxygen (2:1) atmosphere, *N*,*N*-dialkylnaphthylamines were transformed into the corresponding *N*-alkyl-substituted benzo[*cd*]indol-2(1*H*)-ones in 37−71% yields.

In order to enrich the availability of benzo[*cd*]indol-2(1*H*)-ones and overcome the existing challenges, we report here a cobalt-catalyzed C−H carbonylation of naphthylamides for the synthesis of various free (*NH*)-benzo[*cd*]indol-2(1*H*)-ones. With TFBen as a solid and easy manipulation CO source, moderate to high yields of the desired products can be isolated. Additionally, this procedure has been applied successfully in the total synthesis of BET bromodomain inhibitors A and B as well.

Initially, *N*-(naphthalen-1-yl)picolinamide **1a** was chosen as the model substrate for the catalytic system establishing studies. We used **1a** to react with TFBen (3.0 equiv) in the presence of $CoCl_2$ (30 mol %) as the catalyst and Ag_2CO_3/air as the oxidant at 130 °C for 20 h. Fortunately, the expected product **2a** was obtained in 38% yield (Table 1, entry 1). The reaction with $Co(OAc)_2{\cdot}4H_2O$ and $Co(acac)_2$ (Table 1,

Received: June 13, 2019

DOI: 10.1021/acs.orglett.9b02037
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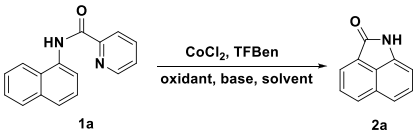
Table 1. Screening of the Reaction Conditions[a]



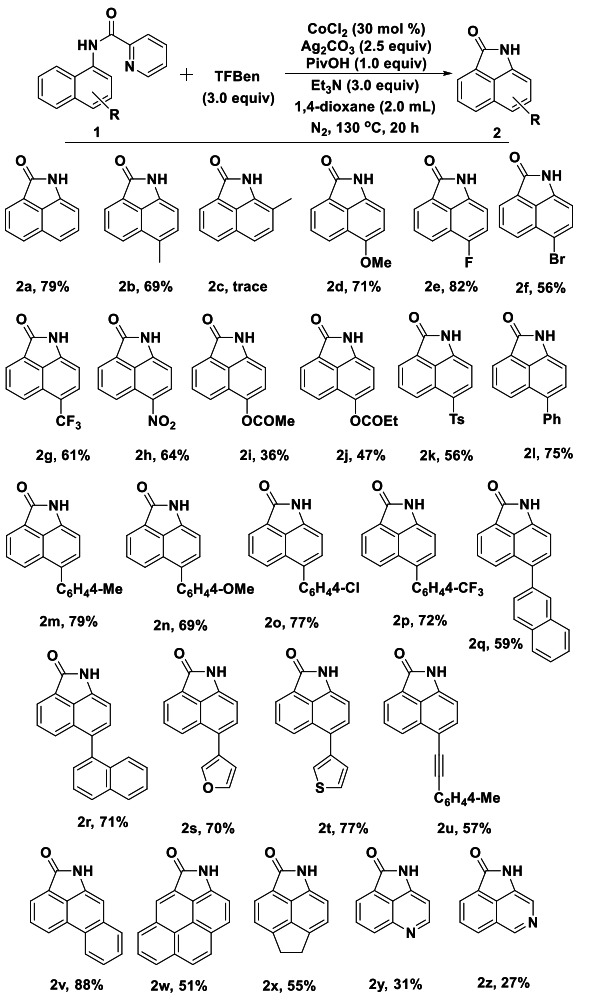
entry	catalyst	oxidant	base	addition	yield[b] (%)
1	$CoCl_2$	Ag_2CO_3/air	Et_3N		38
2	$Co(OAc)_2 \cdot 4H_2O$	Ag_2CO_3/air	Et_3N		16
3	$Co(acac)_2$	Ag_2CO_3/air	Et_3N		30
4	$CoCl_2$	Ag_2CO_3/air	$CsCO_3$		0
5	$CoCl_2$	Ag_2CO_3/air	KO^{t}Bu		trace
6	$CoCl_2$	Ag_2CO_3/air	DMAP		11
7	$CoCl_2$	Ag_2CO_3/N_2	Et_3N		42
8	$CoCl_2$	Ag_2O/N_2	Et_3N		13
9	$CoCl_2$	BQ/N_2	Et_3N		trace
10[c]	$CoCl_2$	Ag_2CO_3/N_2	Et_3N		55
11[c,d]	$CoCl_2$	Ag_2CO_3/N_2	Et_3N	TFA	trace
12[c,d]	$CoCl_2$	Ag_2CO_3/N_2	Et_3N	AcOH	50
13[c,d]	$CoCl_2$	Ag_2CO_3/N_2	Et_3N	PivOH	82 (79[e])
14[c,d]	$CoCl_2$	Ag_2CO_3/N_2	Et_3N	$PhCO_2H$	46
15[c,d,f]	$CoCl_2$	Ag_2CO_3/N_2	Et_3N	PivOH	69

[a]Reaction conditions: **1a** (0.2 mmol), TFBen (3.0 equiv), catalyst (30 mol %), oxidant (1.5 equiv), base (3.0 equiv), solvent (2.0 mL), 130 °C, 20 h. [b]Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]Oxidant (2.5 equiv). [d]Additive (1.0 equiv). [e]Isolated yield. [f]Catalyst (20 mol %).

entries 2 and 3) gave reduced yields. Next, a set of bases was tested, and much lower yields of **2a** were achieved (Table 1, entries 4−6). In addition, when other solvents were used instead of 1,4-dioxane, inferior results were observed. No product could be detected when DMSO or THF was used as the solvent. In the cases of using toluene and MeCN as the reaction media, 27% and 20% yields can be obtained, respectively. It was noteworthy that using Ag_2CO_3 as a sole oxidant under N_2 atmosphere improved the yield to 42% (Table 1, entry 7). Moreover, changing the oxidant to Ag_2O or BQ hampered the reaction (Table 1, entries 8 and 9). We were delighted to find that increasing the amount of Ag_2CO_3 (2.5 equiv) enhanced the reaction outcome, and 55% yield could be reached (Table 1, entry 10). Finally, a series of acidic additives were screened (Table 1, entries 11−14). Gratifyingly, employing PivOH as the additive significantly promoted the reaction to access **2a** in 79% isolated yield (Table 1, entry 13). When the amount of $CoCl_2$ was reduced, a lower yield of **2a** was produced, even in the presence of ligands (Table 1, entry 15). Notably, the model system was tested at 110 and 150 °C as well. A decreased yield (75%) was obtained at 110 °C, and the yield could be slightly improved by performing the reaction at 150 °C (85%). However, considering the energy cost, we decided to continue with 130 °C. The reaction can provide half conversion after 1 h; the prolonged reaction time is to make sure the conversion is complete.

With the optimal reaction conditions in hand, we began exploring the scope of this carbonylative transformation of naphthylamides, and the results are summarized in Scheme 2.

Scheme 2. Scope of Naphthylamides[a]



[a]Reaction conditions: **1** (0.2 mmol), TFBen (3.0 equiv), $CoCl_2$ (30 mol %), Ag_2CO_3 (2.5 equiv), Et_3N (3.0 equiv), 1,4-dioxane (2.0 mL), 130 °C, 20 h, isolated yields.

Naphthylamides with electron-donating groups at the C4 position could undergo the reaction smoothly to give the desired products **2b** and **2d** in high yields. Interestingly, a compound bearing a methyl group at the C2 position gave only a trace amount of product **2c**, suggesting that the steric effect plays an important role in this directing-group-assisted carbonylation. For compounds with halogen substituents, the reaction can also gave the expected products **2e** and **2f** in good yields. It was found that the reaction of substrates with other electron-withdrawing functional groups such as $-CF_3$, $-NO_2$, −OCOMe, −OCOEt, and −Ts proceeded well to afford the corresponding products **2g−k** in 36−64% yields. Both electron-donating and electron-withdrawing groups on the benzene ring of 4-phenyl-substituted naphthylamides were well tolerated to give the desired products **2l−2p** in high yields. When 4-naphthyl-substituted naphthylamides were subjected to the reaction conditions, good yields of the corresponding

DOI: 10.1021/acs.orglett.9b02037
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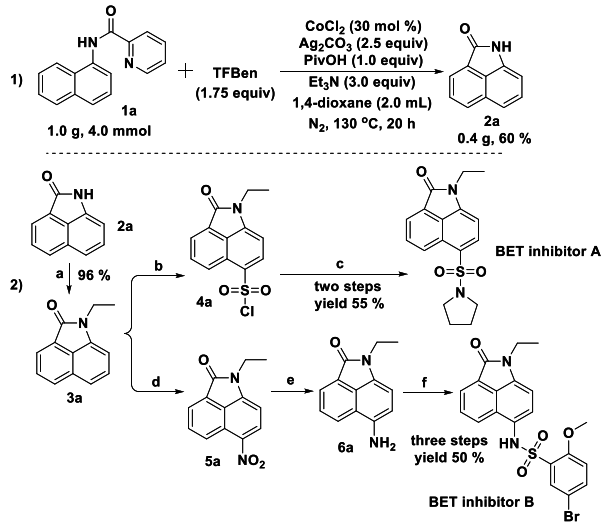
products **2q** and **2r** were achieved. Notably, compounds containing furan and thiophene led to the formation of the desired products **2s** and **2t** in good yields as well. The reaction of substrate bearing an alkyne unit at the C4 position afforded the desired product **2u** in 88% yield. For compounds (**1v** and **1w**) having more conjugated systems, product **2v** and **2w** were obtained in 88% and 51% yields, respectively. Additionally, disubstituted naphthylamide gave the expected product **2x** in 55% yield. Remarkably, the reaction conditions could be applied to substrates with a quinoline and isoquinoline scaffold, albeit in low yields (**2y** and **2z**).

To demonstrate the scalability and utility of this method, we conducted a gram-scale experiment and also completed the total synthesis of BET bromodomain inhibitors A and B (Scheme 3). The naphthylamide **1a** (1.0 g) was treated with

Scheme 3. Large-Scale Reaction and Total Synthesis of BET Bromodomain Inhibitors A and B[a]

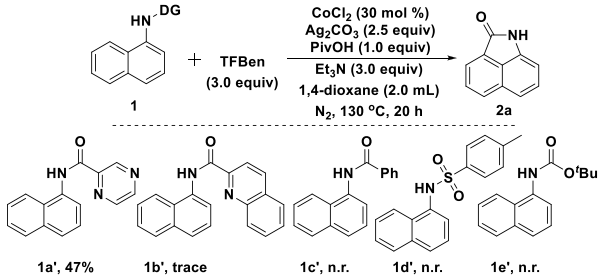


[a]Reagents and conditions: (a) CH_3CH_2I, NaH, DMF, rt; (b) HSO_3Cl, $CHCl_3$, 0−50 °C; (c) pyrrole, DiPEA, CH_2Cl_2, rt; (d) HNO_3, AcOH, 0−50 °C, 1 h; (e) Fe, NH_4Cl, AcOH, 50 °C, 30 min; (f) 5-bromo-2-methoxybenzenesulfonyl chloride, CH_2Cl_2, pyridine, rt.

TFBen (1.75 equiv) under our standard conditions, furnishing the expected (*NH*)-benzo[*cd*]indol-2(1*H*)-one **2a** in 60% yield (0.4 g; Scheme 3, eq 1). Then alkylation of **2a** resulted in formation of the *N*-substituted benzo[*cd*]indol-2(1*H*)-one **3a**. In the total synthesis of BET bromodomain inhibitors A and B, treatment of **3a** with chlorosulfonic acid gave the sulfonyl chloride **4a**, which was then reacted with pyrrole to access BET inhibitor A in 55% yield in two steps (Scheme 3, eq 2a). Additionally, **3a** was reacted with nitric acid to produce **5a** in 69% yield. Subsequent nitro reduction of **5a** with iron formed **6a** in 81% yield. Finally, when **6a** was treated with 5-bromo-2-methoxybenzenesulfonyl chloride, BET inhibitor B was achieved smoothly in 50% yield in three steps (Scheme 3, eq 2b).

Furthermore, we then turned to investigate the effect of directing groups in this C−H carbonylation of naphthylamides. A variety of directing groups were introduced to free naphthylamine and subjected to the standard conditions (Scheme 4). It showed that pyrazine **1a′** containing an additional N atom on the pyridine ring afforded the product **2a** in 47% yield. Interestingly, quinolone-2-carboxamide **1b′** gave

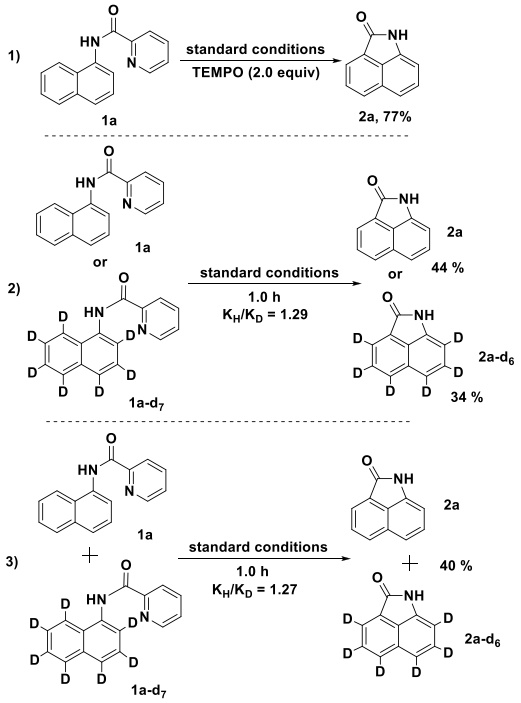
Scheme 4. Effect of Directing Groups in C−H Carbonylation of Naphthylamides



only a trace of **2a**, which could be attributed to the steric hindrance. It was notable that no reaction occurred when Bz as the directing group was employed. These results indicated that the coordination of the cobalt catalyst with a N atom on the directing group was crucial in C−H carbonylation of naphthylamides. Additionally, the reactions of compounds bearing other directing groups such as Ts or Boc failed to proceed.

In order to gain some insight into the reaction mechanism, several control experiments were performed (Scheme 5). First,

Scheme 5. Control Experiments



with the addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as the radical scavenger under our standard reaction conditions, the desired product **2a** was obtained in 77% yield (Scheme 5, eq 1). This results indicating that radical process did not involve in this reaction. Second, the k_H/k_D value of 1.29 was observed when two parallel reactions with **1a** and **1a-*d*$_7$** were carried out (Scheme 5, eq 2). Finally, the intermolecular competition experiment afforded the corresponding products **2a** and **2a-*d*$_6$** and gave the k_H/k_D value of 1.27 (Scheme 5, eq 3). These KIE experiments indicated that the C−H bond-cleavage step might not be involved in the rate-determining step.

DOI: 10.1021/acs.orglett.9b02037
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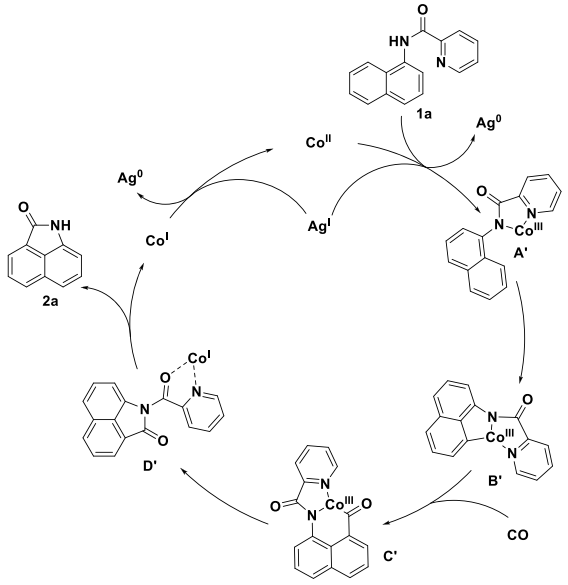
On the basis of the previous reports[10−12] and the control experiments, a plausible mechanism is proposed to account for the C−H carbonylation of naphthylamides (Scheme 6).

Scheme 6. Plausible Reaction Mechanism



Initially, the Co(II) catalyst coordinates with the naphthylamide **1a** and is then oxidized by Ag(I) salt to generate the Co(III) complex **A′**. Subsequently, selective C−H bond activation at the C8 position of **1a** leads to the formation of intermediate **B′**. Then coordination of CO, generated in situ from TFBen, gives the acyl Co(III) species **C′**, which can undergo reductive elimination to form the Co(I) complex **D′**. Finally, hydrolysis of **D′** affords the expected product **2a** and releases the Co(I) species. Oxidation of the Co(I) species by Ag(I) salt regenerates the active Co(II) catalyst.

In conclusion, we have developed an interesting traceless directing-group-assisted cobalt-catalyzed C−H carbonylation of naphthylamides using TFBen as the CO source to access free (*NH*)-benzo[*cd*]indol-2(1*H*)-ones.[13] This protocol features a wide substrate scope and provides a facile and efficient method for the total synthesis of BET bromodomain inhibitors A and B. Further mechanistic studies and synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02037.

General comments, general procedure, optimization details, analytic data and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Zhejiang Natural Science Fund for Young Scholars (LQ18B020008), Zhejiang Sci-Tech University (17062078-Y), and National Natural Science Foundation of China (21772177).

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