Cobalt-Catalyzed Switchable [4 + 1] and [4 + 1 + 1] Spirocyclization of Aromatic Amides with 2-Diazo-1H-indene-1,3(2H)-dione: Access to Spiro Indene-2,1'-isoindolinones and Spiro Isochro-man-3,1'-isoindolinones

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Abstract

Herein we report a condition-controlled divergent synthesis of spiro indene-2,1'-isoindolinones and spiro isochroman-3,1'-isoindolinones through cobalt-catalyzed formal [4 + 1] and [4 + 1 + 1] spirocyclization of aromatic amides with 2-diazo-1H-indene-1,3(2H)-dione. When the reaction is carried out under air in ethyl acetate, spiro indene-2,1'-isoindolinones are formed through Co(II)-catalyzed C-H/N-H [4 + 1] spirocyclization. When the reaction is run under O2 in CH3CN, on the other hand, spiro isochroman-3,1'-isoindolinones are generated through Baeyer-Villiger oxidation of the in situ formed spiro indene-2,1'-isoindolinones with O2 as a cheaper and environmental-friendly oxygen source. In general, these protocols have advantages such as using non-precious and earth-abundant metal catalyst, no extra additive, high efficiency and regioselectivity. A gram-scale synthesis and the removal of the directing group further highlight its utility.

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Cobalt-Catalyzed Switchable [4 + 1] and [4 + 1 + 1] Spirocyclization of Aromatic Amides with 2-Diazo-1*H* -indene-1,3(2*H*)-dione: Access to Spiro Indene-2,1'-isoindolinones and Spiro Isochroman-3,1'-isoindolinones

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Keywords

Spiro indene-2,1'-isoindolinones | Spiro isochroman-3,1'-isoindolinones | Cobalt-catalyzed | Switchable [4 + 1] and [4 + 1 +

Comprehensive Summary

Herein we report a condition-controlled divergent synthesis of spiro indene-2,1'-isoindolinones and spiro isochroman-3,1'-isoi

Background and Originality Content

Spirocyclic skeletons have attracted tremendous interest among synthetic and medicinal chemists, not only

due to their peculiar high rigidity and unique three-dimensional geometries, but also because they are ubiquitous in natural products and possess multiple pharmaceutical activities.[1] In particular, spiro-isoindolinone is an important scaffold that constitutes the core structure in biologically active molecules endowed with anticancer, aldose reductase inhibiting, and TNF-α inhibiting activities (Figure 1).[2] Owing to its significance, the development of practical and economical methods for the preparation of spiro-isoindolinone derivatives have always attracted considerable interest for the synthetic community.[3]

Figure 1 Bioactive molecules containing spiro isoindolinone moieties.

In recent years, directing group-assisted C-H bond activation (CHA) strategy catalyzed by transition metal (TM) has evolved into one of the practical tools for the construction of C-C and C-heteroatom bond due to its excellent atom- and step-economy.[4] In particular, as the high natural abundance of the first row (3d) transition metals renders the catalytic process cost-effective, it is a great privilege to develop earth-abundant metal-catalyzed inert CHA system performing reactions with common substrates.[5] In this regard, cobalt has emerged as a versatile, efficient and less toxic metal-catalyst for CHA to construct polycyclic molecular frameworks.[5-6] On the other hand, *a* -diazo carbonyl compounds have been frequently used as intriguing coupling partners in CHA through dediazonization to generate metal-carbene species with high flexibility and diverse reactivity for the synthesis of various organic functional molecules.[7] However, cobalt-catalyzed CHA carbene insertion reaction has not been well exploited owing to lack of efficient catalytic systems, and most of these transformations were promoted by cyclopentadienyl (Cp*) Co(III) complexes, rather than cheap and commercially available cobalt salt. Based on the fact that 8-aminoquinoline moiety are effective bidentate directing group and can be conveniently removed, it has been used as a popular directing group in TM-catalyzed CHA reactions.[8] Recently, Li and co-workers developed a unique strategy to provide a controllable α- or β-functionalization of α-diazoketones with aromatic amides for the synthesis of isoindolinones via using a non-Cp* cobalt catalyst under ligand-free conditions (Scheme 1a).[9] Very recently, Song's group disclosed an efficient $Co(acac)_2$catalyzed three-component coupling of benzamides with diazo compounds and *tert* -butyl hydroperoxide, providing products with a quaternary carbon center in moderate to excellent yields (Scheme 1b).[10] However, the cobalt-catalyzed C-H bond activation/spiroannulation reaction using diazo compound as carbene precursor to construct spirocyclic framework has not been reported. Enlightened by the aforementioned research and as a continuation of our interest in TM-catalyzed CHA[11] and diazo chemistry,[12] we envisaged a tentative plan to obtain spiro indene-2,1'-isoindolinones from Co-catalyzed [4 + 1] spiroannulation reaction of aromatic amides with 2-diazo-1*H* -indene-1,3(2*H*)-dione. Experimental studies showed that the reaction could selectively furnish the initially designed spirocyclic product through [4 + 1] spiroannulation or the unexpected spiro isochroman-3,1'-isoindolinone derivative through [4 + 1 + 1] oxidative spirocyclization under different reaction conditions. Notably, the formation of spiro isochroman-3,1'-isoindolinone derivatives should involve a Baeyer-Villiger oxidation of the in situ formed spiro indene-2,1'-isoindolinones with O_2 as a cheaper and cleaner oxygen source (Scheme 1c). It is worth mentioning that $[Cp^*RhCl_2]_2$, $[Cp^*IrCl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ were found to be inactive in the oxidative spiroannulation process. To the best of our knowledge, such reaction patterns have not been disclosed previously. Herein, we would like to report the detailed results.

Scheme 1 Co-catalyzed CHA of aromatic amides with diazo compounds

Results and Discussion

At the outset of our studies, the reaction feasibility was tested using 8-aminoquinolinebenzamide (**1a**) with 2-diazo-1*H* -indene- 1,3(2*H*)-dione (**2**) as the model substrates in the presence of 10 mol % $[Cp^*Co(CO)I_2]_2$and 2 equiv. of Ag_2CO_3 in 1,2-dichloroethane (DCE) at 100 °C for 15 h (Table 1, entry 1). It is gratifying that the desired product was obtained in 18% yield as a white solid. Inspired by this positive result, we then screened other simple cobalt salts including $Co(OAc)_2$, $Co(acac)_2$, $Co(acac)_3$ and $Co(NO_3)_2 \cdot 6H_2O$ (Table 1, entries 2-5). Among them, $Co(acac)_2$ was the most effective catalyst that outperformed others to deliver **3a**in 86% yield. Subsequently, we tested various solvents (toluene, CH_3CN, tetrahydrofuran (THF), dioxane, ethyl acetate (EA), CH_3OH) as alternative solvents, and the results confirmed that EA was the most appropriate solvent for this [4 + 1] oxidative spirocyclization (Table 1, entries 6-11). Next, Ag_2O, AgOAc, $Cu(OAc)_2$

and $Mn(OAc)_2$ were tried as oxidant in place of Ag_2CO_3. It turned out that they were less effective (Table 1, entries 12-15). As for the loading of oxidant, we found that using 3 equiv. of Ag_2CO_3increased the yield of **3a** to 97% (Table 1, entries 16-17). Moreover, decreasing or increasing the reaction temperature did not give better yield of **3a** (Table 1, entries 18-19). Furthermore, it should be noted that the reaction run in CH_3CN or dioxane not only afford **3a** in 57% and 73% yields, but also generate another unexpected spiro product **4a** in 26% and 19% yields, respectively (Table 1, entries 7 and 9). It should be noteworthy that the structure of **4a** was ascertained by X-ray single-crystal diffraction (see the SI). This interesting result prompted us to have a further optimization study with the prospect to find suitable reaction conditions to realize selective and efficient synthesis of **4a** . When the reaction was carried out in the presence of 3 equiv. of oxidant in CH_3CN for 24 h, the yield of **4a** increased to 41% (Table 1, entry 20). Other oxidant such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),*tert* -butyl hydroperoxide (TBHP) and $K_2S_2O_8$ were found to be ineffective and delivered only product **3a** (Table 1, entries 21-23). To our delight, when this [4 + 1 +1] oxidative spirocyclization reaction was carried out under an oxygen atmosphere,**4a** was generated in 78% yield. In this case, only trace amount of **3a** was detected (Table 1, entry 24).

Table 1 Optimization studies on the formation of **3a**and **4a** [a]

Entry	Catalyst	Oxidant (eq.)	Solvent	Yield (%)[b]	Yield (%)[b]
				3a	**4a**
1[c]	$[Cp^*Co(CO)I_2]_2$	Ag_2CO_3 (2)	DCE	18	0
2	$Co(OAc)_2$	Ag_2CO_3 (2)	DCE	75	0
3	$Co(acac)_2$	Ag_2CO_3 (2)	DCE	86	0
4	$Co(acac)_3$	Ag_2CO_3 (2)	DCE	84	0
5	$Co(NO_3)_2{\cdot}6H_2O$	Ag_2CO_3 (2)	DCE	16	0
6	$Co(acac)_2$	Ag_2CO_3 (2)	Toluene	78	0
7	$Co(acac)_2$	Ag_2CO_3 (2)	CH_3CN	57	26
8	$Co(acac)_2$	Ag_2CO_3 (2)	THF	51	trace
9	$Co(acac)_2$	Ag_2CO_3 (2)	Dioxane	73	19
10	$Co(acac)_2$	Ag_2CO_3 (2)	EA	89	trace
11	$Co(acac)_2$	Ag_2CO_3 (2)	CH_3OH	0	0
12	$Co(acac)_2$	Ag_2O (2)	EA	50	trace
13	$Co(acac)_2$	AgOAc (4)	EA	65	trace
14	$Co(acac)_2$	$Cu(OAc)_2$ (4)	EA	0	0
15	$Co(acac)_2$	$Mn(OAc)_2$ (2)	EA	51	0
16	$Co(acac)_2$	Ag_2CO_3 (1)	EA	68	0
17	$Co(acac)_2$	Ag_2CO_3 (3)	EA	97	0
18[d]	$Co(acac)_2$	Ag_2CO_3 (3)	EA	85	0
19[e]	$Co(acac)_2$	Ag_2CO_3 (3)	EA	90	0
20[f]	$Co(acac)_2$	Ag_2CO_3 (3)	CH_3CN	49	41
21[f]	$Co(acac)_2$	TEMPO (3)	CH_3CN	19	0
22[f]	$Co(acac)_2$	TBHP (3)	CH_3CN	81	0
23[f]	$Co(acac)_2$	$K_2S_2O_8$ (3)	CH_3CN	36	0
24[f g]	$Co(acac)_2$	Ag_2CO_3 (3)	CH_3CN	trace	78

[a] Reaction conditions: Unless otherwise mentioned, 0.2 mmol of **1a** , 0.3 mmol of **2** , 0.04 mmol of catalyst, 1.5 mL of solvent, 100 °C, air, 15 h.[b] Isolated yields. [c]0.01 mmol of catalyst was used. [d] 80 °C.[e] 120 °C. [f] 24 h.[g] Under O_2.

With the optimal reaction conditions in hand, we first studied the substrate scope of the [4 + 1] spirocyclization reaction by reacting various aromatic amides (**1**) with **2** (Scheme 2). The results demonstrated that substrate **1** with either an electron-donating group (EDG) such as methoxy, *tert* -butyl, methyl and

phenyl or electron-withdrawing group (EWG) such as halides, trifluoromethyl as the R^1 unit attached on the 4-pisition of the phenyl ring worked smoothly to give the desired products (**3b** -**3i**) in good to excellent yields. In following study, it was found that substrates **1** bearing 3- methoxy, 3-methyl, 3-chloro and 3-bromo substituted phenyl scaffold coupled readily with **2** , delivering products**3j** -**3m** in good yields, respectively, at the less hindered position in a highly regioselective manner. The structure of**3k** was confirmed by single-crystal X-ray diffraction analysis (see the SI). Moreover, the reaction of substrates **1** having 2-methyl, 2-chloro or 2-bromo substituted phenyl ring with **2**afforded the corresponding [4 + 1] spiroannulation products in diminished yields probably due to the steric perturbation of these substrates (**3n** -**3p**). Additionally, the reaction of*N* -(quinolin-8-yl)-2-naph- thamide and*N* -(quinolin-8-yl)-1-naphthamide with **2** also proceeded smoothly to generate **3q** and **3r** in 89% and 54% yields, respectively. Furthermore, we were pleased to find that 5-methoxyquinolin-8-amine and 5-chloroquinolin- 8-amine as directing groups were also compatible with this transformation to afford**3s** and **3t** in good yields. Unfortunately, 2-methoxy-*N* -(quinolin-8-yl)benzamide and*N* -(quinolin-8-yl)furan -2-carboxamide failed to provide the desired product, presumably because of the coordination of the oxygen with the Co-catalyst. In addition, 2-diazocyclopentane-1,3-dione and 2-diazocyclohexane- 1,3-dione could not participate in this reaction under the standard conditions.

Scheme 2 Substrate scope for the synthesis of**3** [a ,b]

[a] Reaction conditions: Unless otherwise mentioned, 0.2 mmol of **1a** , 0.3 mmol of **2** , 0.04 mmol of $Co(acac)_2$, 0.6 mmol of Ag_2CO_3, 1.5 mL of EtOAc, 100 °C, air, 15 h. [b] Isolated yields.[c] under Ar.

Next, we investigated the substrate scope of the [4 + 1 + 1] spirocyclization reaction for the preparation of spiro isochroman-3,1'-isoindolinone **4** (Scheme 3). Various aromatic amides **1** bearing diverse functional groups such as methoxy,*tert* -butyl, methyl, phenyl fluoro, chloro, or bromo, trifluoromethyl on the *para* -, *meta* -, or *ortho* -site of phenyl moiety smoothly underwent the [4 + 1 + 1] spirocyclization reactions, delivering products **4b** -**4p** in moderate to good yields. Of note, 2-methyl, 2-fluoro, 2-chloro, or 2-bromo substituted *N* -(quinolin-8-yl)benzamides reacted with **2**under standard conditions for the formation of **4a** , furnishing the corresponding products **4m** -**4p** in 58-70% yields. We assumed that under the conditions of generating **4** , the solvent CH_3CN could replace quinolin-8-amine serve as a ligand for the Co-catalyst, reducing the influence of steric hindrance effect. To our delight, the developed methodology is also applicable for*N* -(quinolin-8-yl)-1-naphthamide,*N* -(5-methoxyquinolin-8-yl) benzamide and*N* -(5-chloroquinolin-8-yl)benzamide giving corresponding annulated product **4q** -**4s** in good yields.

In order to get more insights into the reaction mechanism, a series of control experiments were conducted (Scheme 4). First, deuterium incorporation experiments were performed by treating **1a** with CD_3OD or D_2O under the standard conditions for **3a** , and the results showed that no H/D exchange was detected. Furthermore, the same results were observed when treating**1a** and **2** with CD_3OD or D_2O under the standard conditions. These results indicated that the C-H bond cleavage is irreversible (Scheme 4a). Second, the intermolecular competition reaction of the 1:1

Scheme 3 Substrate scope for the synthesis of**4** [a ,b]

[a] Reaction conditions: 0.2 mmol of **1a** , 0.3 mmol of **2a** , 0.04 mmol of $Co(acac)_2$, 0.6 mmol of Ag_2CO_3, 1.5 mL of CH_3CN, 100 degC, O_2, 24 h.[b] Isolated yields.

mixture of methoxy substituted benzamide (**1b**) and trifluoromethyl substituted benzamide (**1i**) with **2** gave a mixture of **3b** and **3i** in 18% and 17% yields, respectively. This outcome suggests that electron-rich substrate is slightly favorable for this reaction than an electron-deficient one (Scheme 4b). Third, an intermolecular competitive reaction was performed by treating an equimolar mixture of **1a** and**1a-d_5** with **2** , from which**3a** and **3a-d_4** were gained in a ratio of 0.53:0.47 upon analyzing ^1H NMR spectra, and competitive kinetic isotope effect (KIE) value of 1.13 was calculated, revealing that the C(sp^2)-H bond activation might not be involved in the turnover-limiting step (Scheme 4c).

Furthermore, to testing the proposal that **4a** might be formed through transformation of **3a** , we performed a series of control experiments (Scheme 5). Firstly, **3a** was subjected to the standard reaction conditions

for the formation of **4a** , affording**4a** in 87% yield. In contrast, under Ar atmosphere, **4a**was not observed (Scheme 5a and 5b). Secondly, **4a** was generated in 84% yield in the presence of 0.5 eq. Ag_2CO_3 and O_2. However, no desired product was yielded in the absence silver salt (Scheme 5c and 5d). Finally, **3a** could not be converted **4a** under standard conditions in the presence of radical scavengers such as TEMPO and BHT (2,6-di-tert-butyl-4-methylphenol) (Scheme 5e). These results showed that **4a** was formed by oxygen participation in Baeyer-Villiger oxidation of **3a** promoted by Ag^+.

On the basis of control experiments and known reports,[9-13] a plausible mechanism for the cobalt-catalyzed [4 + 1] and [4 + 1 + 1] spirocyclization reactions have been depicted in Scheme 6. At first, the coordination of the two nitrogen atom of **1a** to a Co(III) complex generated via oxidant by Ag_2CO_3 forms the five-membered cobaltacycle intermediate **I** , which undergoes the concerted metalation-deprotonation pathway to give intermediate**II** . The coordination of **2** to the metal center in**II** followed by release of N_2 affords the cobalt-carbene species intermediate **III** . Subsequently,

Scheme 4 Mechanistic studies (I)

Scheme 5 Mechanistic studies (II)

the migratory insertion yields intermediate **IV** , which undergoes reductive elimination to form the [4 + 1] spirocyclization product**3a** and delivers Co(I) complex, which is then reoxidized to regenerate the active Co(III) species. In another aspect, under the promotion of Ag^+ and O_2, the in situ formed **3a** undergoes a Baeyer-Villiger oxidation to generate the product **4a** .[13]

To demonstrate the synthetic utility of the current protocol, the large scale experiment and directing group removal experiment were performed. As shown in Scheme 7a and 7b, a mixture of **1a** (3 mmol) and**2a** (4.5 mmol) was subjected to the aforementioned both standard reaction conditions, yielding the [4 + 1] and [4 + 1 + 1] spirocyclization products **3a** and **4a** in 80% and 62% yields, respectively. On the other hand, **3s** and **4r**could be easily transformed into spiro[indene-2,1'-isoindoline]-1,3,3'-trione **5** and spiro[isochroman-3,1'-isoindoline]-1,3',4-trione **6** through removing the 5-methoxyquinolin-8-amine directing group in moderate overall yields, respectively (Scheme 8).

Scheme 6 Proposed mechanism

Scheme 7 Enlarged scale synthesis of **3a** and

5a

Scheme 8 Removal of directing group

Conclusions

In summary, we have reported condition controlled Co(II)-catalyzed selective [4 + 1] and [4 + 1 + 1] spirocyclization reactions of aromatic amides with 2-diazo-1*H* -indene-1,3(2*H*)-dione leading to the construction of spiro indene-2,1'-isoindolinones and spiro isochroman-3,1'-isoindolinones. This current protocol features with earth-abundant and cheap metal catalyst, avoidance of external additives, low-cost, clean and abundant oxygen source, and valuable products with moderate to excellent yields. Moreover, gram-scale synthesis and the removal of the directing group further demonstrate the practicability of this protocol to potential industrial applications.

Experimental

General procedure for the synthesis of 3

To a reaction tube equipped with a stir bar were added*N* -(quinolin-8-yl)benzamide (**1a** , 50 mg, 0.2 mmol), 2-diazo-1*H* -indene-1,3(2*H*)-dione (**2** , 52 mg, 0.3 mmol), $Co(acac)_2$ (10 mg, 0.04 mmol), Ag_2CO_3 (165 mg, 0.6 mmol) and ethyl acetate (1.5 mL). The tube was then sealed, and the mixture was stirred at 100 degC (metal module heating) under air for 15 h. Upon completion, it was cooled to room temperature, filtered through a pad of celite, and concentrated under reduced pressure. The residue was purified by silica gel

column chromatography using petroleum ether/ethyl acetate (3:1) as eluent to afford **3a** . Other products **3b -3t**were obtained in a similar manner.

General procedure for the synthesis of 4

To a reaction tube equipped with a stir bar were added*N* -(quinolin-8-yl)benzamide (**1a** , 50 mg, 0.2 mmol), 2-diazo-1*H* -indene-1,3(2*H*)-dione (**2** , 52 mg, 0.3 mmol), $Co(acac)_2$ (10 mg, 0.04 mmol), Ag_2CO_3 (165 mg, 0.6 mmol) and CH_3CN (1.5 mL). The tube was then sealed, and the mixture was stirred at 100 degC (metal module heating) under O_2 for 24 h. Upon completion, it was cooled to room temperature, filtered through a pad of celite, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/ethyl acetate (3:1) as eluent to afford **4a** . Other products **4a-4s** were obtained in a similar manner.

Synthesis of spiro[indene-2,1'-isoindoline]-1,3,3'-trione (5)

i) 2'-(5-Methoxyquinolin-8-yl)spiro[indene-2,1'-isoindoline]- 1,3,3'-trione (**3s** , 84 mg, 0.2 mmol) was placed in a 10 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. DCM (1.0 mL) was sequentially injected via a syringe. To the suspension was added BBr_3 (0.24 mL, 1M in THF, 0.24 mmol) at 0 degC (ice-water bath). The mixture was stirred at 0 degC (ice-water bath) for 5 min and then allowed to warm to room temperature for 18 h. The resulting mixture was quenched with water at 0 degC and extracted with ethyl acetate three times. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4.

ii) The crude product dissolved in MeCN/H_2O (MeCN/H_2O = 4:1, 2 mL), $Ce(NH_4)_2(NO_3)_6$(CAN, 658 mg, 1.2 mmol) was added to the mixture with a portion at room temperature, and the mixture was stirred for 12 h at 60 degC (oil bath). After the reation completed, H_2O (5 mL) was added and the mixture was extracted with ethyl acetate (3 mL x3). Combined organic phase was dried over anhydrous Na_2SO_4, filtered through Celite and the filtrate was concentrated. The crude residue was purified by flash chromatography in petroleum ether:ethyl acetate= 1:1 to give **5** as white soild (27 mg, 51%).

Synthesis of spiro[isochroman-3,1'-isoindoline]-1,3',4-trione (6)

i) 2'-(5-methoxyquinolin-8-yl)spiro[isochroman-3,1'-isoindo- line]-1,3',4-trione (**4r** , 87 mg, 0.2 mmol) was placed in a 10 mL two-necked reaction flask, which was filled with nitrogen by using the standard Schlenk technique. DCM (1.0 mL) was sequentially injected via a syringe. To the suspension was added BBr_3 (0.24 mL, 1M in THF, 0.24 mmol) at 0 degC (ice-water bath). The mixture was stirred at 0 degC (ice-water bath) for 5 min and then allowed to warm to room temperature for 18 h. The resulting mixture was quenched with water at 0 degC and extracted with ethyl acetate three times. The combined organic layer was washed with water and dried over anhydrous Na_2SO_4.

ii) The crude product dissolved in MeCN/H_2O (MeCN/H_2O = 4:1, 2 mL), $Ce(NH_4)_2(NO_3)_6$(CAN, 658 mg, 1.2 mmol) was added to the mixture with a portion at room temperature, and the mixture was stirred for 12 h at 60 degC (oil bath). After the reation completed, H_2O (5 mL) was added and the mixture was extracted with ethyl acetate (3 mL x3). Combined organic phase was dried over anhydrous Na_2SO_4, filtered through Celite and the filtrate was concentrated. The crude residue was purified by flash chromatography in petroleum ether:ethyl acetate= 1:1 to give **6** as white soild (25 mg, 45%).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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References

1. (a) Zheng, Y.; Tice, C. M.; Singh, S. B. The Use of Spirocyclic Scaffolds in Drug Discovery, *Bioorg. Med. Chem. Lett.***2014**, *24*, 3673–3682. (b) Smith, L. K.; Baxendale, I. R. Total Syntheses of Natural Products Containing Spirocarbocycles,*Org. Biomol. Chem.* **2015**, *13*, 9907–9933. (c) Zheng, Y. J.; Tice, C. M. The Utilization of Spirocyclic Scaffolds in Novel Drug Discovery. Expert. *Opin. Drug. Dis.* **2016**,*11*, 831–834. (d) Hiesinger, K.; Dar'in, D.; Proschak, E.; Krasavin, M. Spirocyclic Scaffolds in Medicinal Chemistry. *J. Med. Chem.* **2021**, *64*, 150–183.
2. (a) Sharma, S.; Oh, Y.; Mishra, N. K.; De, U.; Jo, H.; Sachan, R.; Kim, H. S.; Jung, Y. H.; Kim, I. S. Rhodium-Catalyzed [3 + 2] Annulation of Cyclic *N*-Acyl Ketimines with Activated Olefins: Anticancer Activity of Spiroisoindolinones. *J. Org. Chem.***2017**, *82*, 3359–3367. (b) Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D. Novel SpiroSuccinimides with Incorporated Isoindolone and Benzisothiazole 1,1-Dioxide Moieties as Aldose Reductase Inhibitors and Antihyperglycemic Agents. *J. Med. Chem.* **1992**, *35*, 4613–4627. (c) Chia, Y. C.; Chang, F. R.; Wu, C. C.; Teng, C. M.; Chen, K. S.; Wu, Y. C. Effect of Isoquinoline Alkaloids of Different Structural Types on Antiplatelet Aggregation in vitro. *Planta Med.* **2006**, *72*, 1238–1241. (d) Wang, J.; Chen, F.; Liu, Y.; Liu, Y.; Li, K.; Yang, X.; Liu, S.; Zhou, X.; Yang, J. Spirostaphylotrichin X From a Marine-Derived Fungus as an Anti-influenza Agent Targeting RNA Polymerase PB2. *J. Nat. Prod.* **2018**, *81*, 2722–2730.
3. (a) Ding, A.; Meazza, M.; Guo, H.; Yang, J. W.; Rios, R. New Development in the Enantioselective Synthesis of Spiro Compounds.*Chem. Soc. Rev.* **2018**, *47*, 5946–5996. (b) Alves, A. J. S.; Alves, N. G.; Soares, M. I. L.; Melo, T. M. V. D. P. Strategies and Methodologies for the Construction of Spiro-γ-lactams: An Update. *Org. Chem. Front.* **2021**, *8*, 3543–3593.
4. (a) He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J. Q. Palladium-Catalyzed Transformations of Alkyl C-H Bonds. *Chem. Rev.* **2017**, *117*, 8754–8786. (b) Rej, S.; Chatani, N. Rhodium-Catalyzed $C(sp^2)$-or $C(sp^3)$-H Bond Functionalization Assisted by Removable Directing Groups. *Angew. Chem., Int. Ed.***2019**, *58*, 8304–8329. (c) Wu, Y.; Pi, C.; Wu, Y.; Cui, X. Directing Group Migration Strategy in Transition-Metal-Catalysed Direct C-H Functionalization. *Chem. Soc. Rev.* **2021**,*50*, 3677–3689.
5. (a) Su, B.; Cao, Z. C.; Shi, Z. J. Exploration of Earth-Abundant Transition Metals (Fe, Co, and Ni) as Catalysts in Unreactive Chemical Bond Activations. *Acc. Chem. Res.* **2015**, *48*, 886–896. (b) Zweig, J. E.; Kim, D. E.; Newhouse, T. R. Methods Utilizing First-Row Transition Metals in Natural Product Total Synthesis. *Chem. Rev.* **2017**, *117*, 11680–11752. (c) Li, Y.; Hu, Y.; Wu, X. F. Non-Noble Metal-Catalysed Carbonylative Transformations. *Chem. Soc. Rev.* **2018**, *47*, 172–194. (d) Gandeepan, P.; Muller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann. L. 3d Transition Metals for C-H Activation. *Chem. Rev.* **2019**, *119*, 2192–2452.
6. (a) Moselage, M.; Li, J.; Ackermann, L. Cobalt-Catalyzed C-H Activation. *ACS Catal.* **2016**, *6*, 498–525. (b) Kommagalla, Y.; Chatani, N. Cobalt(II)-Catalyzed CAH Functionalization Using an N, N'-Bidentate Directing Group. *Coord. Chem. Rev.***2017**, *350*, 117–135. (c) Cizikovs, A.; Lukasevics, L.; Grigorjeva, L. Cobalt-Catalyzed C-H Bond Functionalization Using Traceless Directing Group. *Tetrahedron* **2021**,*93*, 132307. (d) Banjare, S. K.; Nanda, T.; Pati, B. V.; Biswal, P.; Ravikumar, P. C. *O*-Directed C-H Functionalization*via* Cobaltacycles: A Sustainable Approach for C-C and C-Heteroatom Bond Formations. *Chem. Commun.* **2021**,*57*, 3630–3647.
7. (a) Xiang, Y.; Wang, C.; Ding, Q.; Peng, Y. Diazo Compounds: Versatile Synthons for the Synthesis of Nitrogen Heterocycles *via*Transition Metal-Catalyzed Cascade C-H Activation/Carbene Insertion/Annulation Reactions. *Adv. Synth. Catal.***2019**, *361*, 919–944. (b) Nunewar, S.; Kumar, S.; Talakola, S.; Nanduri, S.; Kanchupalli, V. Co(III), Rh(III) & Ir(III)-Catalyzed Direct C-H Alkylation/Alkenylation/Arylation with Carbene Precursors. *Chem. Asian J.* **2021**, *16*, 443–459. (c) Solovyev, I.; Eremeyeva, M.; Zhukovsky, D.; Dar'in, D.; Krasavin, M. Cyclic Diazo Compounds in the Construction of Spirocyclic Scaffolds. *Tetrahedron Lett.* **2021**, *62*, 152671. (d) Kumar, S.; Nunewar,

S.; Oluguttula, S.; Nanduri, S.; Kanchupalli, V. Recent Advances in Rh(III)/ Ir(III)-Catalyzed C-H Functionalization/Annulation *via* Carbene Migratory Insertion.*Org. Biomol. Chem.* **2021**, *19*, 1438–1458.

8. (a) Berger, M.; Chauhan, R.; Rodrigues, C. A. B.; Maulide, N. Bridging C-H Activation: Mild and Versatile Cleavage of the 8-Aminoquinoline Directing Group. *Chem. -Eur. J.* **2016**, *22*, 16805–16808. (b) Deguchi, T.; Xin, H. L.; Morimoto, H.; Ohshima, T. Direct Catalytic Alcoholysis of Unactivated 8-Aminoquinoline Amides.*ACS Catal.* **2017**, *7*, 3157–3161. (c) Fitzgerald, L. S.; O'Duill, M. L. A Guide to Directing Group Removal: 8-Aminoquinoline. *Chem. -Eur. J.* **2021**, *27*, 8411–8436. (d) Liu, B.; Romine, A. M.; Rubel, C. Z.; Engle, K. M.; Shi, B. F. Transition-Metal-Catalyzed, Coordination-Assisted Functionalization of Nonactivated C(sp^3)-H Bonds.*Chem. Rev.* **2021**, *121*, 14957–15074.
9. Xu, M. R.; Yuan, Y.; Wang, Y.; Tao, Q. H.; Wang, C. Y.; Li, Y. Z. Controllable α- or β-Functionalization of α-Diazoketones with Aromatic Amides via Cobalt-Catalyzed C-H Activation: A Regioselective Approach to Isoindolinones. *Org. Lett.* **2019**, *21*, 6264–6269.
10. Li, M. H.; Si, X. J.; Zhang, H.; Yang, D. D.; Niu, J. L.; Song, M. P. Directed Cobalt-Catalyzed C-H Activation to Form C-C and C-O Bonds in One Pot via Three-Component Coupling. *Org. Lett.* **2021**,*23*, 914–919.
11. (a) Guo, C.; Li, B.; Liu, H.; Zhang, X.; Fan, X. Synthesis of Fused or Spiro Polyheterocyclic Compounds *via* the Dehydrogenative Annulation Reactions of 2-Arylindazoles with Maleimides. *Org. Lett.* **2019**, *21*, 7189–7193. (b) Li, B.; Guo, C. H.; Shen, N. N.; Zhang, X. Y.; Fan, X. S. Synthesis of Maleimide Fused Benzocarbazoles and Imidazo[1,2-*a*]pyridines via Rhodium(III)-Catalyzed [4 + 2] Oxidative Cycloaddition. *Org. Chem. Front.* **2020**, *7*, 3698–3704. (c) Li, H.; Shen, M. Y.; Li, B.; Zhang, X. Y.; Fan, X. S. Solvent-Dependent Selective Synthesis of CF_3-Tethered Indazole Derivatives Based on Multiple Bond Activations. *Org. Lett.* **2023**,*25*, 720–725. (d) Song, X.; Wang, K. L.; Zhang, X. Y.; Fan, X. S. Unsymmetrical Relay C-H Alkenylation and [2 + 2] Cycloaddition of *N*-Arylsydnones with Allenyl Acetates Leading to Quinoline-Fused Cyclobutanes. *Org. Chem. Front.* **2023**,*10*, 1191–1197.
12. (a) Li, B.; Zhang, B. B.; Zhang, X. Y.; Fan, X. S. Regio-selective Synthesis of Diversely Substituted Benzo[*a*]carbazoles through Rh(III)-Catalyzed Annulation of 2-Arylindoles with α-Diazo Carbonyl Compounds. *Chem. Commun.* **2017**, *53*, 1297–1300. (b) Li, B.; Shen, N. N.; Zhang, X. Y.; Fan, X. S. Synthesis of Fused Imidazo[1,2-*a*]pyridines Derivatives through Cascade C(sp^2)-H Functionalizations.*Org. Biomol. Chem.* **2019**, *17*, 9140–9150. (c) Li, B.; Shen, N. N.; Yang, Y. J.; Zhang, X. Y.; Fan, X. S. Synthesis of Naphtho[1',2':4,5]imidazo- [1,2-*a*]pyridines*via* Rh(III)-Catalyzed C-H Functionalization of 2-Arylimidazo[1,2-*a*]pyridines with Cyclic 2-Diazo-1,3-diketones Featuring with a Ring Opening and Reannulation.*Org. Chem. Front.* **2020**, *7*, 919–925. (d) Li, B.; Shen, N. N.; Yang, Y. J.; Zhang, X. Y.; Fan, X. S. Tunable Synthesis of Indeno[1,2-*c*]furans and 3-Benzoylindenones via $FeCl_3$-Catalyzed Carbene/Alkyne Metathesis Reaction of*o*-Alkynylbenzoyl Diazoacetates. *Org. Lett.***2021**, *23*, 388–393. (e) Li, B.; Shen, N. N.; Wang, K. L.; Fan, X. S.; Zhang, X. Y. Rh(III)-Catalyzed Reaction of 2-Aryl-3-acyl-1*H*-indoles with α-Diazo Carbonyl Compounds: Synthesis of 5-Carbonyl Substituted Benzo[*a*]carbazoles*via* [5 + 1] Annulation. *Asian J. Org. Chem.***2022**, *11*, e202100710.
13. (a) Lian, X. L.; Lei, H.; Quan, X. J.; Ren, Z. H.; Wang, Y. Y.; Guan, Z. H. Oxidation of 2-Arylindoles for Synthesis of 2-Arylbenzoxazinones with Oxone as the Sole Oxidant. *Chem. Commun.* **2013**,*49*, 8196–8198. (b) Yamashita, M.; Iida, A. Copper-Mediated Oxidative Tandem Reactions with Molecular Oxygen: Synthesis of 2-Arylbenzoxazinone Derivatives from Indoles. *Tetrahedron Lett.***2014**, *55*, 2991–2993. (c) Feng, Y. D.; Li, Y. D.; Cheng, G. L.; Wang, L. H.; Cui, X. L. Copper-Catalyzed Synthesis of 2-Arylquinazolinones from 2-Arylindoles with Amines or Ammoniums.*J. Org. Chem.* **2015**, *80*, 7099–7107.

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Entry for the Table of Contents

Cobalt-Catalyzed Switchable [4 + 1] and [4 + 1 + 1] Spirocyclization of Aromatic Amides with 2-Diazo-1*H*

Herein we report a condition-controlled divergent synthesis of spiro indene-2,1'-isoindolinones and spiro isochroman-3,1'-isoi