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Rhodium(III)-catalyzed synthesis of spirocyclic isoindole *N*-oxides and isobenzofuranones *via* C–H activation and spiroannulation†

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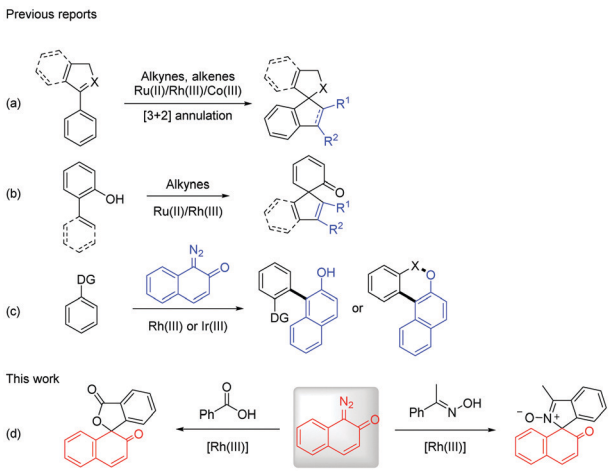
Rhodium(III)-catalyzed mild and oxidative [4+1] spiroannulation has been realized *via* C–H activation of oximes and benzoic acids with 1-diazonaphthelen-2(1*H*)-ones as coupling reagents. This transformation integrates C–H activation and dearomatization and provides a direct approach to spirocyclic isoindole *N*-oxides and isobenzofuranones with functional group tolerance.

Metal-catalyzed and directing group-assisted C–H bond activation has been established as an advantageous strategy for synthesis of a plethora of (hetero)cyclic molecules, including spirocycles.[1] Among these reports, [3+2] cyclization *via* initial C–H bond cleavage of arenes has been widely investigated. In this domain, two distinct synthetic strategies based on coupling with alkynes have been developed on the basis of the intrinsic properties of the arene substrate. The nucleophilicity of *in situ* generated metal alkenyl species electronically matches the electrophilic directing group for annulation (Scheme 1a).[2] Alternatively, dearomative oxidative annulation that employs nucleophilicity of the directing group also serves as an important strategy (Scheme 1b).[3] Despite the progress, the coupling reagents are mostly restricted to alkynes and activated (cyclic) alkenes.[4] Given the synthetic limitations and diverse applications of spirocycles in natural products, biologically active molecules, and functional materials,[5] it is necessary to explore novel and efficient methods to access structurally diverse spirocycles.

On the other hand, diazo compounds are well known as effective coupling reagent in metal-catalyzed C–H activation en route to C–C bond formations.[6] In particular, 1-diazonaphthelen-2(1*H*)-ones as a unique class of diazo compounds have been predominantly used as arylation reagents[7] or occasionally as C3 synthons[8] in Rh(III)- and Ir(III)-catalyzed C–H activation chemistry



Scheme 1 Rh(III)- or Ir(III)-catalyzed C–H activation/annulation.

(Scheme 1c). However, 1-diazonaphthelen-2(1*H*)-ones have been rarely applied as C1 synthons in annulation reactions. Inspired by prior reports, we reasoned that arenes bearing a nucleophilic directing group such as oximes[9] and benzoic acids[10] might participate in C–C coupling and annulation with quinone diazides under oxidative conditions for the synthesis of spirocyclic compounds (Scheme 1d). To implement this concept, the process of C–N or C–O reductive elimination needs to be fast than protonolysis (if it is irreversible). This may be achieved by a judicious choice of the oxidant as well as the arene. We now report Rh(III)-catalyzed oxidative [4+1] spiroannulation of oximes and benzoic acids with 1-diazonaphthelen-2(1*H*)-ones for efficient synthesis of spirocyclic nitrones and isobenzofuranones (Scheme 1d).

Our initial experiments were performed with 1-phenylethan-1-one oxime (**1a**) and 1-diazonaphthelen-2(1*H*)-one (**2a**) in the presence of $[Cp^*RhCl_2]_2$ (4 mol%) and AgOAc (2.0 equiv.) at 50 °C in MeCN (Table 1). To our delight, the spirocyclic nitrone **3aa** was obtained in 61% NMR yield (entry 1). The yield was slightly increased when the temperature was lowered to 40 °C

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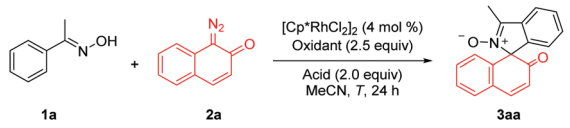
Table 1 Optimization of the reaction conditions[a]



1a 2a 3aa

Entry	Oxidant	Acid	T (°C)	Yield[b] (%)
1	AgOAc	—	50	61
2	AgOAc	—	40	66
3	AgOAc	—	35	64
4	AgOAc	—	25	40
5	AgOAc	PivOH	40	76
6	AgOAc	AcOH	40	66
7	AgOAc	MesCOOH	40	61
8	Ag_2CO_3	PivOH	40	63
9	$Cu(OAc)_2$	PivOH	40	NR
10	AgOPiv	PivOH	40	60
11[c]	AgOAc	PivOH	40	79 (72)[d]
12[e]	AgOAc	PivOH	40	NR

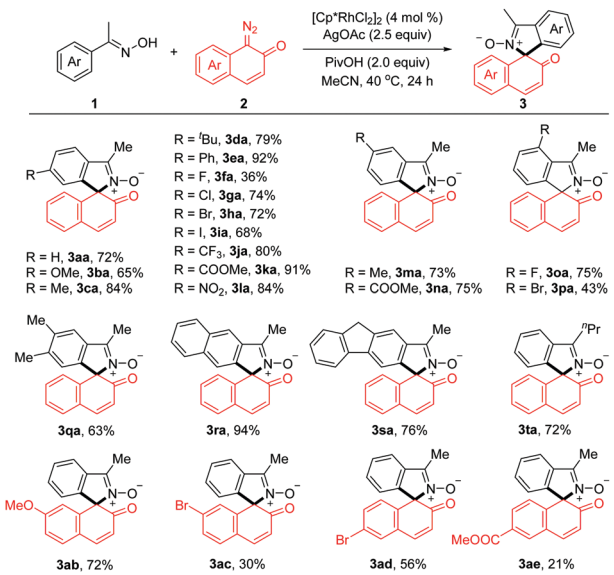
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), Acid (2.0 equiv.), Oxidant (2.0 equiv.), MeCN (2 mL), T °C, 24 h under N_2 in a sealed tube. [b] NMR yield using 1,3,5-trimethoxybenzene as internal standard. [c] AgOAc (2.5 equiv.). [d] Isolated yield after chromatography. [e] Without $[Cp^*RhCl_2]_2$.

(entries 2–4). Introduction of PivOH as an additive led to formation of the spirocyclic product **3aa** in 76% NMR yield (entry 5). Screening of acid additives gave PivOH as the optimal one (entries 6 and 7). What's more, AgOAc proved to be suitable oxidant since other oxidants (Ag_2CO_3, $Cu(OAc)_2$, and AgOPiv) only led to lower coupling efficiency (entries 8–10). A good isolated yield (72%) was obtained when AgOAc (2.5 equiv.) was used (entry 11). Control experiments revealed that no desired transformation occurred in the absence of a Rh(III) catalyst (entry 12).

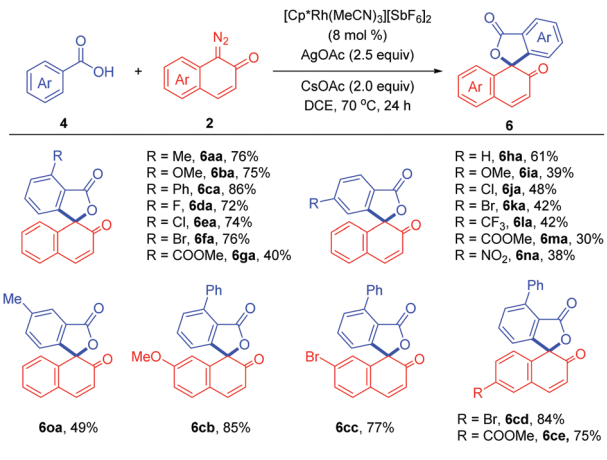
With the optimized reaction conditions in hand, we next examined the scope of the coupling of oximes and quinone diazides (Scheme 2). A range of oximes bearing electron-donating, -withdrawing and halogen groups at the *para* position reacted efficiently with diazonaphthalen-2(1*H*)-one **2a**, affording the corresponding spirocyclic nitrone in 36–92% yields (**3aa–3la**). In addition, methyl (**3ma**), and ester (**3na**) groups at the *meta*-position of the benzene ring were also well tolerated, providing the coupled products in good yields and in excellent regioselectivity (>25 : 1), where C–H activation occurred at the less sterically hindered *ortho* site. *ortho*-Substituted oximes also underwent smooth [4+1] spiroannulation to afford products **3oa** and **3pa** in 43–75% yields. Furthermore, disubstituted oximes (**3qa**, **3sa**), 2-naphthyl oxime (**3ra**) and 1-phenylbutan-1-one oxime (**3ta**) were also suitable substrates. Next, the generality of diazo compounds was briefly investigated. Diazonaphthalen-2(1*H*)-ones bearing electron-donating, -withdrawing, and halogen groups underwent smooth coupling in generally acceptable yields (**3ab–3ae**).

To better define the scope of arenes, benzoic acids were applied under slightly modified conditions, from which spirocyclic isobenzofuranones were isolated in moderate to high yields (Scheme 3). The presence of *ortho* electron-donating, -withdrawing and halogen group on the benzene ring resulted in the formation of the spirocycle in 40–86% yields (**6aa–6ga**), and the product **6ea** was characterized by X-ray crystallography (CCDC 1992558†). However, a few *para*- or *meta*-substituted benzoic acids coupled with **2a** in lower efficiency (**6ha–6oa**) compared with the *ortho*-substituted ones, especially for those with withdrawing groups such as trifluoromethyl (**6la**), ester (**6ma**), and NO_2 (**6na**) presumably because of reduced nucleophilicity of the carboxylic group. Notably, only a single regioisomer was obtained for a *meta*-methyl substituted benzoic acid (**6oa**). The scope of the diazonaphthalen-2(1*H*)-ones was also found to be quite decent (**6ca–6ce**). Introduction of electron-donating, -withdrawing and halogen groups such as methoxy (**6cb**), bromo (**6cc**, **6cd**) and ester (**6ce**) at the C6 and C7 positions of the diazo reagent all resulted in high efficiency.

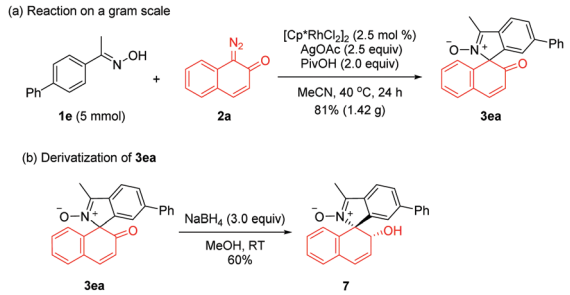
To demonstrate the synthetic utility of the catalytic system, a gram-scale reaction has been realized, and product **3ea** was isolated in 81% yield under reduced catalyst loading (Scheme 4a).



Scheme 2 Rh(III)-Catalyzed [4+1] spiroannulation of oximes. Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (4 mol%), AgOAc (2.5 equiv.), PivOH (2.0 equiv.), MeCN (2 mL) at 40 °C under N_2 for 24 h. Isolated yield.



Scheme 3 Rh(III)-Catalyzed [4+1] spiroannulation of benzoic acids and diazo compounds. Reaction conditions: **4** (0.2 mmol), **2** (0.24 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (8 mol%), AgOAc (2.5 equiv.), CsOAc (2.0 equiv.), DCE (2 mL) at 70 °C under N_2 for 24 h. Isolated yield.

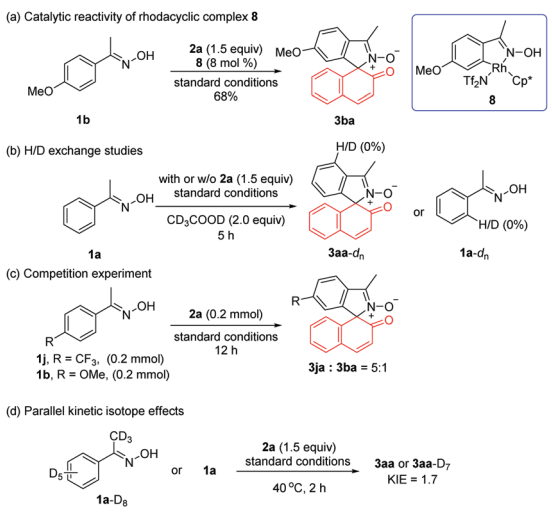


Scheme 4 Synthetic applications.

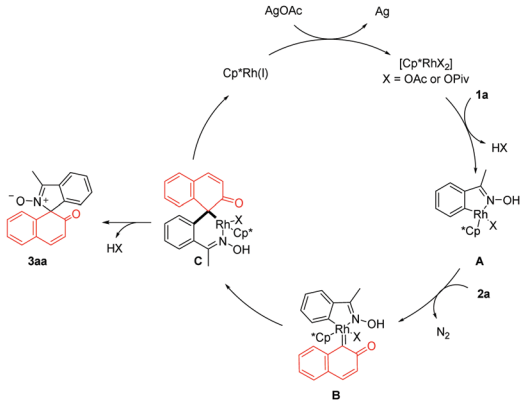
Reduction of **3ea** by $NaBH_4$ delivered the alcohol product **7** in 60% yield as a single diastereomer (Scheme 4b).

Several mechanistic experiments have been carried out to explore the mechanism (Scheme 5). Rhodacyclic complex **8**[11] has been prepared as a catalyst precursor for the coupling of **1b** and **2a**, from which **3ba** was isolated in 68% yield under the standard conditions (Scheme 5a). H/D exchange experiments between **1a** and CD_3COOD in the absence or presence of a coupling partner **2a** were carried out. In either case, no deuterium incorporation at the *ortho* position of **1a** and in the product **3aa** has been observed, suggesting irreversibility of the C–H activation (Scheme 5b). In addition, a competition reaction of oximes **1j** and **1b** with **2a** afforded the corresponding products **3ja** and **3ba** in a ratio of 5 : 1, thus indicating that the C–H activation probably occurs *via* a concerted metalation-deprotonation (CMD) mechanism (Scheme 5c). Meanwhile, the C–H bond cleavage process is probably not involved in the rate-determining step, since an insignificant primary kinetic isotope effect (k_H/k_D = 1.7) was revealed from two parallel experiments (Scheme 5d).

Based on our mechanistic experiments and related reports,[8] a mechanistic pathway is proposed in Scheme 6. Cyclometalation of oxime **1a** affords a rhodacyclic intermediate **A** together with generation of an acid. Subsequent coordination and decomposition of the diazo compound **2a** gives a rhodium carbene species **B**. Migratory insertion of the Rh-aryl bond then produces rhodium(III)



Scheme 5 Mechanistic studies.



Scheme 6 Proposed catalytic cycle.

enolate species **C**. Reductive elimination and elimination of HX delivers the final product **3aa** and a Cp*Rh(I) intermediate, which is then oxidized by AgOAc to regenerate the active Rh(III) catalyst.

In summary, we have realized Rh(III)-catalyzed oxidative [4+1] spiroannulation of oximes and benzoic acids using 1-diazonaphthelen-2(1*H*)-ones as an efficient C1 reagent, which provides an efficient procedure for the synthesis of two classes of spiroheterocycle. This annulation system proceeded with high functional group compatibility under mild conditions. The oxime functionality and the carboxylic group function as a nucleophilic directing group. Further studies on other important spirocyclization reactions are underway in our laboratory.

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Conflicts of interest

There are no conflicts of interest to declare.

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