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One-pot synthesis of 2,3-disubstituted dihydrobenzofurans and benzofurans *via* rhodium-catalyzed intramolecular C–H insertion reaction[†]

Xueji Ma,^a Feifei Wu,^a Xiaofei Yi,^a Hangxiang Wang*^{bc} and Wanzhi Chen*^a

Intramolecular sp³ C–H insertion reaction of α -imino rhodium carbene generated from *N*-sulfonyl-1,2,3-triazoles has been described. A number of 2,3-dihydrobenzofuran and benzofuran derivatives have been obtained in good to excellent yields.

Benzofuran and dihydrobenzofuran are versatile building blocks in organic synthesis and key structures of numerous natural products with biological activities.¹ Numerous efforts have been made to construct benzofuran and dihydrobenzofuran skeletons. Several classic strategies are available including intramolecular Friedel-Crafts reaction and Wittig reaction.² Moreover, transition-metal-catalyzed C-C and C-O formation reactions represent atom-economic protocols for the construction of benzofuran moieties.³ For instance, 2,3-disubstituted benzofurans can be synthesized from o-functionalized phenols and their derivatives through palladium-, copper-, platiniumand silver-catalyzed annulation reactions.^{3a-g} Metal carbenoids, especially rhodium carbenoids, generated from diazo compounds, have been applied to the synthesis of dihydrobenzofuran motifs (Scheme 1, eqn (1)), but only limited examples were reported.⁴ The need to develop novel and efficient approaches to synthesize benzofurans is still required.

Recently, *N*-sulfonyl-1,2,3-triazoles have emerged as alternative precursors for the formation of metallocarbenes.⁵ The α -imino carbenes derived from *N*-sulfonyl triazoles are capable of undergoing a variety of useful reactions, including the synthesis of N-heterocycles,⁶ stereoselective cycloadditions,⁷ C–H bond insertion,^{60,p,8} X–H bond insertion (X = heteroatoms),⁹ and other transformations.¹⁰ The C–H bond insertion reactions of α -imino carbenes leading to heterocyclic compounds and enamides were



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Scheme 1 Metal carbenoid strategy for synthesis of benzofurans.

restricted to electron rich sp² C–H bonds.^{60,p,8b,c} So far only one example of sp³ C–H insertion of α -imino rhodium carbenes was reported to give β -chiral sulfonamides.^{8a} Herein, we wish to report the synthesis of 2,3-dihydrobenzofuran and benzofuran derivatives *via* the intramolecular sp³ C–H insertion reactions of α -imino rhodium carbenes.

Our initial studies began with the intramolecular C–H bond insertion reaction of 4-(2-(benzyloxy)phenyl)-1-tosyl-1*H*-1,2,3-triazole **1a**. Using Rh₂(Oct)₄ as the catalyst, ring-opening of the triazole and subsequent insertion of the α -imino carbene towards the C–H bond adjacent to oxygen took place leading to **2a** in 51% yield as a mixture of two *E*/*Z* isomers together with trace amounts of **3a** at 90 °C (Scheme 2).

Compound 2a bearing an interesting exocyclic double bond and versatile functional groups might be utilized for rapid construction of molecular complexity. Approaches to synthesize such a skeleton were quite limited so far.¹¹ We optimized the reaction conditions. $Rh_2(OAC)_4$ and $Rh_2(OPiv)_4$ are also active



Scheme 2 Rh(II)-catalyzed intramolecular C-H bond insertion of 1a.

^a Department of Chemistry, Zhejiang University, Hangzhou 310028, China.

E-mail: chenwzz@zju.edu.cn

^b The First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, 310003, China. E-mail: wanghx@zju.edu.cn

^c Collaborative Innovation Center for Diagnosis and Treatment of Infectious

Diseases, Zhejiang University, Hangzhou, 310003, China

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 a Reaction conditions: 1 (0.5 mmol), Rh_2(S-PTV)_4 (1 mol%), CH_2Cl_2 (4 mL), 90 $^\circ$ C, 2 h, under N2. b 4 h.

giving **2a** in 30% and 57% yields. Electron-deficient $Rh_2(TFA)_4$ is totally inactive. Bulky ligands containing Hashimoto-type catalysts could significantly improve the reaction, and **2a** could be obtained in 91% yield in CH_2Cl_2 with 1 mol% of $Rh_2(S-PTV)_4$ as the catalyst (see Table S1 in the ESI†). CH_2Cl_2 is the most appropriate solvent. As demonstrated in Table 1, under the optimized conditions, **2a–2b** were isolated in *ca*. 90% yields as mixtures of two isomers with E/Z ratios of 72:28 and 61:39, respectively. Due to the steric effect, the E/Z ratio was increased to 85:15 for **2c**. In the cases of **1e–1g** bearing more steric substituents, almost pure (*E*)-isomers of **2e–2g** could be isolated after simple chromatography. Unexpectedly, only (*Z*)-isomer of **2h** was obtained in 64% yield.

Interestingly, we found that catalytic hydrogenation of 2a in the presence of 5 mol% of Pd/C catalyst and 1 atm H_2 at 45 $^{\circ}C$ did not give the expected 2,3-dihydrobenzofuran, instead, benzofuran 4a was obtained almost quantitatively. Moreover, we found that 4a could be obtained in a one-pot manner without isolation of 2a. After completion of rhodium-catalyzed C-H insertion reaction of 1, Pd/C was added to the mixture and switched to a H₂ atmosphere, 4a-s were directly afforded in good to excellent yields. The results were summarized in Table 2. For substrates 1b-1c containing a methyl at 3- or 4-postions of the benzyl groups, the reactions proceeded smoothly to give the corresponding products 4b and 4c in excellent yields (88 and 91%). However, when electron-withdrawing Cl was introduced at the *para*-position of the benzyl group, the yield of 4d was sharply decreased to 68% due to the impaired electronic density. Similar results were observed when Cl, F, CF₃ and OMe were at meta positions of the benzyl groups. In the case of 1i bearing a methoxy at the para position of the benzyl group, 4i was obtained in only 57% yield, and obvious decomposition of the starting Table 2Scope of the reaction for the synthesis of 4^a



^{*a*} Reaction conditions: under N₂, **1** (0.5 mmol), Rh_2 (S-PTV)₄ (1 mol%) and CH_2Cl_2 (4 mL) were stirred in a sealed tube at 90 °C for 2 h. Then 5 mol% of Pd/C was added, and the mixture was stirred at 45 °C under H₂ for 3 h. ^{*b*} 4 h. ^{*c*} 70 °C.

material was observed. However, the methoxy at the *meta* position has less influence.

Probably due to the steric effect, the *tert*-butyl group failed to increase the yield of 4j. The steric effect was quite obvious when the benzyl groups containing F and Cl groups at their ortho positions, and the corresponding products 4k and 4l were afforded in 54 and 37% yields, respectively, even the reaction time was elongated to 4 hours. The intramolecular C-H insertion of 1m and 1n were also studied. The corresponding benzofuran 4m was delivered in moderate yield, but the reaction of 1n was sluggish to give the desired product in a very poor yield. The results indicate that the primary C-H bond is much inert than the secondary C-H bond and benzyl C-H bonds. In sharp contrast, 40 was obtained in excellent yield even the reaction temperature was lowered to 70 °C. Under the same conditions, other substrates containing additional methyl, ethyl and Cl groups on the phenyl ring gave corresponding benzofurans 4p-4r in good to excellent yields.



^{*a*} Reaction conditions: under N₂, **1** (0.5 mmol), Rh₂(S-PTV)₄ (1 mol%) and CH₂Cl₂ (4 mL) were stirred in a sealed tube at 90 °C for 2 h. Then 5 mol% of the Pd/C catalyst was added, and the mixture was stirred at 45 °C for 3 h. ^{*b*} 4 h.



However, a bulky *tert*-butyl group retarded the reaction and only 45% yield was obtained.

The formation of **4** appears to proceed *via* the insertion of α -imino rhodium carbene towards a C–H bond adjacent to oxygen and subsequent isomerization of the double bond in the presence of a Pd/C catalyst. However, when the reaction was carried out under a N₂ atmosphere instead of H₂, the isolated **2** was transformed into benzofuranyl imine **3** rather than **4** in the presence of Pd/C in CH₂Cl₂ or EtOH. This indicates that the transformation of **2** to **4** is not a simple isomerization process. Similarly, **3** could also be obtained from **1** *via* the one pot, two-step process in a N₂ atmosphere. The results are summarized in Table **3**. The overall yields depend on the carbene insertion reaction of C–H bonds.

A proposed catalytic pathway for the formation of **4** is outlined in Scheme 3. First, reaction of triazole **1** with the Rh(π) complex would generate α -imino rhodium carbene species, and intramolecular C–H insertion would give 2,3-dihydrofuran **B** *via* a three-centered transition state **A**.¹² The imine **B** is not stable, and a rapid [1,3]-H shift would occur giving more stable **2**. We assumed that **4** was formed *via* palladium-catalyzed dehydrogenation and hydrogenation. Oxidative addition of sulfonamide N–H would produce Pd–H species **C**.¹³ After reductive elimination, **3** is formed. Finally, hydrogenation of **3** could give **4**.



Scheme 4 Further transformation of 3c and 4h into aldehyde and azepine.

The reactive imino groups of compound **3** can be transformed into other functional groups (Scheme 4). Treatment of **3c** with K_2CO_3 in methanol at room temperature afforded benzofuran-3carbaldehyde **5**. Moreover, treatment of **4h** with formaldehyde in dichloromethane at room temperature could give tetracyclic azepine **6** in 88% yield. Regioisomers of **6** and **6**' were isolated in a ratio of 1.2:1. The present strategy offers a rapid synthetic route of polycyclic azepines in excellent yields. Further effort is required to increase the regioselectivity of the products.

In conclusion, we have described a facile route for the synthesis of 2,3-dihydrobenzofurans and benzofurans. The reactions proceed *via* rhodium-catalyzed ring-opening of *N*-sulfonyl-1,2,3-triazles, the intramolecular sp³ C–H insertion reaction of α -imino rhodium carbene, and subsequent palladium-catalyzed dehydrogenation. 2,3-Disubstituted hydrobenzofurans and benzofurans can be obtained in good to excellent yields in a one-pot manner.

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