

Controllable Rh(III)-Catalyzed Annulation between Salicylaldehydes and Diazo Compounds: Divergent Synthesis of Chromones and Benzofurans

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(5) Supporting Information



ABSTRACT: A Rh(III)-catalyzed annulation between salicylaldehydes and diazo compounds with controllable chemoselectivity is described. AgNTf₂ favored benzofurans via a tandem C–H activation/decarbonylation/annulation process, while AcOH led to chromones through a C–H activation/annulation pathway. The reaction exhibited good functional group tolerance and scalability. Moreover, only a single regioisomer of benzofuran was obtained due to the in situ decarbonylation orientation effect.

I n the last two decades, transition-metal-catalyzed C–H activation has been well studied and identified as one of the most powerful tools in organic synthesis.¹ Ideally, the structurally diverse products could be achieved from the same materials via selective C–H functionalization in a controllable manner. Recently, advances have been achieved through the choice of catalysts,² ligands,³ directing groups,⁴ and electronic/steric effects.⁵ Although the aforementioned methods have been widely investigated, the continuous development of new methods to precisely control the product distribution in C–H activation is still a hot research topic and challenging problem for chemists.

Salicylaldehydes are versatile building blocks in organic synthesis, and numerous endeavors have been devoted to functionalizing salicylaldehydes with alkenes, alkynes, and allenes via a direct aldehydic C-H activation and/or annulation process.⁶ The key to the success of these works was the formation of a five-membered-ring organometallic intermediate as shown in Scheme 1a. On the other hand, the synthetic applications of the exotic oxa-metallacycles⁷ formed through decarbonylative metalation of salicylaldehydes in annulation have remained unexplored until now⁸ (Scheme 1b). To fulfill this objective, predictable challenges might be met: (1) how to regulate the selectivity to realize the facile decarbonylation in the presence of the direct aldehydic C–H functionalization and (2) whether the four-membered oxa-metallacycle generated from decarbonylation exhibits sufficient stability to achieve the subsequent annulation process. On the basis of our continuous interest in transition-metal-catalyzed selective C-H activation and diazo compounds⁹ and also to enrich the reaction type of salicylaldehydes, herein we report our results on a Rh(III)catalyzed tandem C-H activation, decarbonylation, and

Scheme 1. Transition-Metal-Catalyzed C–H Activation of Salicylaldehydes

a) Previous work: aldehydic C-H activation and direct functinalization



annulation between salicylaldehydes and diazo compounds¹⁰ toward the construction of benzofurans and chromones in a controllable manner (Scheme 1c). It is necessary to point out that in our reaction the decarbonylation plays an important role in orientation to achieve a single regioisomer of benzofuran, which overcomes the regioselective problems faced by employing phenols as coupling reactants.¹¹ Moreover, the competitive reaction between the formed metal carbenoid intermediate and the phenolic hydroxyl group of salicylaldehydes has also been well suppressed.¹²

We set out our investigation with salicylaldehyde 1a and ethyl 2-diazo-3-oxobutanoate 2a as model substrates. A preliminary



attempt with 2.5 mol % of $[RhCp*Cl_2]_2$ and 20 mol % AgOAc in 2 mL of DCE at 50 °C offered the decarbonylation/annulation product **3aa** in 21% yield with the direct aldehydic C–H activation/annulation product **4aa** in 55% yield (Table 1, entry

Table 1. Optimization of Reaction Conditions⁴

| ОН | + Me N ₂ COOEt <u>cataly</u> | rst/additive | Me + COOE |
|-----------------|---|--------------------|---------------------------------------|
| 1a | 2a | 3aa | 4aa |
| entry | catalyst | additive | yield (3aa/4aa) ^b |
| 1 | [RhCp*Cl ₂] ₂ | AgOAc | 21/55 |
| 2 | $[RhCp*Cl_2]_2$ | AgSbF ₆ | 52/31 |
| 3 | $[RhCp*Cl_2]_2$ | $AgBF_4$ | 43/0 |
| 4 | $[RhCp*Cl_2]_2$ | AgNTf ₂ | 90 (87) ^c /0 |
| 5 ^d | $[RhCp*Cl_2]_2$ | AgNTf ₂ | 69/0 |
| 6 ^e | $[RhCp*Cl_2]_2$ | AgNTf ₂ | 56/0 |
| 7 | $[RhCp*Cl_2]_2$ | AcOH ^f | 0/44 |
| 8 | $[RhCp*Cl_2]_2$ | PivOH ^f | 0/32 |
| 9 | [RhCp*Cl ₂] ₂ | MSA ^f | 0/0 |
| 10 ^g | $[RhCp*Cl_2]_2$ | AcOH ^f | 0/82 ^c |
| 11 | | AgNTf ₂ | 0/0 |
| 12 | | AcOH ^f | 0/0 |
| | | | |

^{*a*}Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2a** (1.0 mmol, 2.0 equiv), catalyst (0.0125 mmol, 2.5 mol %), additive (20 mol %), DCE (2 mL), 50 °C, 12 h under air atmosphere. ^{*b*}Yields were determined by ¹H NMR using dibromomethane (δ = 4.80) as an internal standard. ^{*c*}Isolated yields. ^{*a*}10 mol % of AgNTf₂ was used. ^{*e*}Room temperature. ^{*f*}2.0 equiv of additives. ^{*g*}80 °C.

1). When $AgSbF_6$ was tested, **3aa** could be produced in 52% yield (Table 1, entry 2). The yield of **3aa** was further increased to 90% when $AgNTf_2$ was used (Table 1, entry 4). Decreasing the amount of $AgNTf_2$ or reducing the reaction temperature led to lower yields (Table 1, entries 5 and 6). To improve the yield of **4aa**, some additives were then examined. When AcOH was used, **4aa** could be furnished in 44% yield with a certain amount of **1a** and **2a** unconverted (Table 1, entry 7). By further increasing the temperature to 80 °C, the yield of **4aa** was promoted to 82% (Table 1, entry 10). Neither **3aa** nor **4aa** could be obtained without the loading of [RhCp*Cl₂]₂ (Table 1, entries 11 and 12).

With the optimized conditions in hand, the substrate scope for the synthesis of benzofurans was examined as shown in Table 2. When 5-methoxysalicylaldehyde was investigated, 3ca was obtained in 78% yield. 5-Halogen-substituted products 3da-fa were prepared in 61-69% yields. In previous works,¹² when 3substituted phenols were used as coupling reactants, it was difficult to obtain a single regioisomer of 4-substituted or 6substituted benzofuran. Here, our methods provided a practical way to settle this problem with the in situ decarbonylation orientation effect. When 4-methylsalicylaldehyde was tested, only 6-methylbenzofuran 3ha was obtained, and the structure was identified by single-crystal X-ray analysis.¹³ Salicylaldehydes with substituents at the C3 or C6 positions performed smoothly to offer 3ja-la in 82-93% yields. 1-Hydroxy-2-naphthaldehyde 1p delivered 3pa in 78% yield. Considering that the benzofuran skeleton is widespread in drugs and natural products, late-stage modification of estrone and tyrosine were tested, and the desired products 3qa and 3sa were prepared in 71% and 79% yields. Compound 3ra,¹⁴ identified as a COX-1 and COX-2 inhibitor, was also synthesized conveniently in 57% yield. When the ester group of 2a was altered from an ethyl group to methyl, isopropyl,



Table 2. Substrate Scope for the Synthesis of Benzofurans a,b

^{*a*}Reaction conditions: 1 (0.5 mmol, 1.0 equiv), 2 (1.0 mmol, 2.0 equiv), $[RhCp^*Cl_2]_2$ (0.0125 mmol, 2.5 mol %), AgNTf₂ (20 mol %), DCE (2 mL), 50 °C for 12 h under air atmosphere. ^{*b*}Isolated yields.

benzyl, and allyl groups, 3ab-af were obtained in 81-90% yields. When the R² group was replaced with ethyl, *n*-propyl, and cyclopropyl groups, 3ag-ai were prepared in 80-88% yields. 2-Unsubstituted and 2-phenyl-substituted 3ak and 3al were obtained in 72% and 69% yields. When the reaction was scaled up to 10 mmol, 3aa could be prepared in 71% yield (1.45 g).

The substrate scope for the synthesis of chromones was then examined, and the results are shown in Table 3. 5-Methyl- and 5methoxysalicylaldehydes gave 4ba and 4ca in 85% and 90% yields. Salicylaldehydes with halogen groups at the C5 position offered 4da and 4fa in 83% and 79% yields. Compound 4ga with a strong electronic-withdrawing group (NO₂) was obtained in 50% yield. The C3- or C4-substituted salicylaldehydes offered the corresponding products in 80-87% yields. 6-Hydroxybenzo-[d] [1,3] dioxole-5-carbaldehyde delivered **4ma** in 70% yield. Substrates with phenyl and 2-thienyl groups at the C5 position yielded 4na and 4oa in 68% and 60% yields. When 1-hydroxy-2naphthaldehyde 1p was examined, 4pa was obtained in 58% yield. Estrone and tyrosine derivatives 4qa and 4sa with a chromone skeleton were prepared in 80% and 91% yields. Methyl, tert-butyl, and benzyl 2-diazo-3-oxobutanoates yielded 4ab, 4ad, and 4ae in 81%, 77%, and 82% yields. Alkyl- and arylsubstituted diazo compounds in the R² position offered 4ag, 4ah,



Table 3. Substrate Scope for the Synthesis of Chromones a,b

^{*a*}Reaction conditions: 1 (0.5 mmol, 1.0 equiv), 2 (1.0 mmol, 2.0 equiv), $[RhCp*Cl_2]_2$ (0.0125 mmol, 2.5 mol %), AcOH (2.0 equiv), DCE (2 mL), 80 °C for 12 h under air atmosphere. ^{*b*}Isolated yields.

and **4al** in 80%, 79%, and 49% yields. Ethyl 2-diazo-3oxopropanoate **1k** gave **4ak** in 90% yield. Compound **4aj** with a chloro group in the R² position was obtained in 70% yield. When 3-diazopentane-2,4-dione **2m** was tested, **4am** was obtained in 94% yield. Flavone derivative **4an**¹⁵ with antityrosine-kinase activity could be prepared in 64% yield. When the model reaction was conducted on a 10 mmol scale, **4aa** was obtained in 1.74 g (74% yield).

On the basis of our control experiments (see the Supporting Information for details) and previous reports,¹⁶ the plausible reaction pathway for the Rh(III)-catalyzed annulation between salicylaldehydes and diazo compounds with controllable chemoselectivity is proposed as shown in Scheme 2. When AgNTf₂ is used as an additive (Scheme 2a), the cationic complex Cp*Rh(III) is generated, participating in the directed C–H activation of salicylaldehyde to offer intermediate **A**. Catalyst with a weaker coordinating counterion (such as Tf₂N⁻) prefers the decarbonylation, while the stronger counterions (Cl⁻, AcO⁻) are unlikely to fulfill this role.¹⁷ We speculated that the Ag⁺ may also play an important role in promoting the decarbonylation process, while the specific role is unclear at the present stage. A sequential decarbonylation process occurs to generate the four-

Scheme 2. Plausible Reaction Pathway



membered oxa-metallacycle B, which reacts with 2a to offer the Rh-carbene complex C with the release of N₂. Then the intermediate D is generated after the migratory insertion process, which is protonated to form E with the regeneration of the active rhodium catalyst. Later, the intramolecular dehydration condensation of E yields the product 3aa. When AcOH was used as the additive (Scheme 2b), the hydroxyl-directed C-H activation of 1a affords the intermediate F, which reacts with 2a directly to produce a five-membered-ring Rh-carbene complex G. Next, the migratory insertion yields intermediate H, which is then protonated to form I with the regeneration of the active catalyst. Chromone 4aa is achieved through the intramolecular dehydration condensation of intermediate I.

In conclusion, we have developed a rhodium-catalyzed annulation between salicylaldehydes and diazo compounds with controllable chemoselectivity. AgNTf₂ favored benzofurans via a tandem C-H activation/decarbonylation/annulation process, while AcOH led to chromones through a C-H activation/annulation pathway. The reaction exhibited good functional group tolerance and scalability, and only a single regioisomer of benzofuran was obtained due to the in situ decarbonylation orientation effect. To expand the application of our method, late-stage modification was conducted to provide estrone and tyrosine derivatives with chromone and benzofuran skeletons in high efficiency, and two reported bioactive molecules were also conveniently synthesized. The preliminary mechanism study illustrated that a four-membered oxa-metallacycle might be generated during the C-H activation/decarbonylation step.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03355.

¹H and ¹³C NMR spectra for all new compounds (PDF) X-ray crystallographic data for **3ha** (CIF)

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Notes

The authors declare no competing financial interest.

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