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<td>Author(s)</td>
<td>Yang, Junfeng; Yoshikai, Naohiko</td>
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Cobalt-Catalyzed Annulation of Salicylaldehydes and Alkynes to Form Chromones and 4-Chromanones**

Junfeng Yang and Naohiko Yoshikai[a]

Abstract: Unique reaction manifolds of cobalt(I)–diphosphine catalytic systems have been identified in the coupling of salicylaldehyde (SA) and an internal alkyne, which affords a dehydrogenative annulation product (chromone) or a reductive annulation product (4-chromanone) depending on the alkyne substituents. Distinct from related rhodium(I)– and rhodium(III)-catalyzed reactions of SA and alkynes, these annulation reactions feature aldehyde C–H oxidative addition of SA and subsequent hydrometalation of the C–O bond of another SA molecule as a common key step. The reductive annulation to 4-chromanones also involves the action of Zn as a stoichiometric reductant. Besides these mechanistic features, the present Co catalysis is complementary to the Rh(1) and Rh(II)-catalyzed reactions of SA and internal alkynes, particularly in the context of chromone synthesis.

The catalytic coupling of aldehydes and unsaturated hydrocarbons via transition metal-mediated aldehyde C–H activation represents an atom-efficient synthetic approach to ketones.[11] Such reactions often employ chelating aldehydes to facilitate the C–H activation and to prevent decarbonylation of the resulting acetylmetal species. Among various chelating aldehydes, salicylaldehyde (SA) is particularly attractive for its ready availability as well as for the frequent occurrence of ortho-hydroxy or -alkoxy acrylcarbonyl motifs in natural products and bioactive substances. Indeed, hydroacylation and related acylation reactions of SA have been developed using alkynes.[2–5] alkynes,[2b,6,7] and allenes[2b,8] as the reaction partners, most extensively using rhodium catalysts. As an illustrative example, Miura and coworkers demonstrated two distinct reaction manifolds for the coupling of SA and an internal alkyne under Rh(1) or Rh(II) catalysis (Scheme 1a). A Rh(I)–diphosphine catalyst promotes a standard hydroacylation process through C–H oxidative addition, alkyne insertion into Rh–H, and C–C reductive elimination to afford an α,β-unsaturated ketone.[2a,b] On the other hand, a Rh(II) catalyst, in the presence of a Cu(I) oxidant, effects oxidative annihilation through deprotonative C–H metatation, alkyne insertion into Rh–C, and C–O reductive elimination to afford a chromone derivative.[5]

Recently, we have found that Co(I)–diphosphine catalysts serve as viable alternatives to Rh(I)–diphosphine catalysts for the intramolecular hydroacylation of 2-acylbenzaldehydes and 2-alkenylbenzaldehydes.[5,10] We have also developed another Co(I)–diphosphine catalyst as an alternative to the Wilkinson catalyst for the intermolecular olefin hydroacylation using a chelating aldehyde.[11][12] Along with this line of research, we became interested in the ability of a Co(I) catalyst to effect activation and transformation of SA. We report here that Co–dpye (1,2-bis(dicyclohexylphosphino)ethane) catalytic systems promote annihilation reactions of SA and internal alkynes to afford chromone or 4-chromanone derivatives depending on the alkyne substituents (Scheme 1b). Both the reactions commonly feature the expense of another molecule of SA as an acceptor of the aldehyde hydrogen presumably through a C–H oxidative addition/C–O hydrometalation sequence, while the latter annihilation involves the action of Zn as a stoichiometric reductant. Besides such mechanistically distinct features compared with the Rh(I) catalysis, the Co(I) catalysis is complementary to the Rh(II) catalysis as a method for the synthesis of chromones, which represent core structures of flavonoids, isoflavonoids, and related bioactive compounds.[14]

Scheme 1. Transition metal-catalyzed reactions of salicylaldehyde and alkyne.
hydroacylation product in any of our screening experiments. Instead, a catalyst generated from CoBr₂ (10 mol%), dcpp (10 mol%), and Zn (50 mol%) promoted the reaction of excess 1a (0.3 mmol) and 2a (0.1 mmol) in DMSO at 80 °C (conditions A), affording a chromone derivative 3aa in 82% yield, along with a substantial amount (0.079 mmol) of 2-hydroxybenzyl alcohol (4a) (Table 1, entry 1). The latter product apparently indicated that 1a acted not only as a reactant but also as a hydrogen acceptor (vide infra), and indeed the yield of 3aa dropped significantly when 1a was used as a limiting reagent.¹⁵ The reaction is highly dependent on the ligand. Thus, the yield of 3aa dropped drastically using other typical diphosphine or monophosphine ligands (entries 2–6). The use of Mn or In as an alternative reducend resulted in a lower yield of 3aa (entries 7 and 8). The reaction became sluggish in other solvents such as THF and MeCN (entries 9 and 10).

### Table 1. Effect of reaction conditions on dehydrogenative annulation of salicylaldehyde (1a) and alkyne 2a.⁶

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from conditions A[a]</th>
<th>Yield of 3aa [%][b]</th>
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<tr>
<td>1</td>
<td>none</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>dppp instead of dcpp</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>dcpp instead of dcpp</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>dppe instead of dcpp</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>dpf instead of dcpp</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>PCY₂ instead of dcpp</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Mn instead of Zn</td>
<td>41</td>
</tr>
<tr>
<td>8</td>
<td>In instead of Zn</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>THF instead of DMSO</td>
<td>8</td>
</tr>
<tr>
<td>10</td>
<td>MeCN instead of DMSO</td>
<td>0</td>
</tr>
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[a] The reaction was performed on a 0.1 mmol scale. [b] Abbreviations: dcpp = 1,2-bis(diphenylphosphino)propane; dcpp = 1,3-bis(diphenylphosphino)propane; dcpp = 1,1′-bis(diphenylphosphino)ferrocene; dppe = 1,1′-bis(diisopropylphosphino)ferrocene; determined by GC using n-tridecane as an internal standard. [c] 20 mol% of PCY₂ was used.

With the Co–dcpp catalytic system in hand, we explored the scope of the dehydrogenative annulation (Scheme 2). A variety of 1-aryl-2-silylacetylenes participated in the reaction with 1a to regioselectively afford the corresponding 2-aryl-3-silylchromones 3aa–3al, with tolerance of functional groups including methoxy, hydroxy, fluoro, ester, and ketone groups. Besides the 1-aryl-2-silylacetylenes, silylacetylenes bearing alkenyl and alkyl groups also underwent regioselective dehydrogenative annulation to afford the corresponding dicarbocyclic derivatives 3am–3ap. The catalytic system was also applicable to dialkylalkynes such as 4-octyne (see 3ap).

Reactions of SAs substituted at the 3, 4, or 5-position with 2a proceeded smoothly, thus affording the corresponding chromones 3ba–3la in moderate to good yields. By contrast, 6-methoxysalicylaldehyde failed to participate in the dehydrogenative annulation with 2a, presumably due to steric repulsion of the methoxy and the formyl groups, which would interfere with the formation of a metalacycle intermediate (vide infra).

During exploration of the scope of alkynes in the dehydrogenative annulation, we found that the reaction of 1a and 1-phenyl-1-propyne (2q) under the conditions A regioselectively produced a 4-chromanone derivative 5aq in a modest yield of 32% with only a trace amount of the expected chromone derivative 3aq (Scheme 3a). Upon further modification of the reaction conditions, the yield of 5aq could be improved to 73% using the same precatalysts along with a catalytic amount (20 mol%) of Na₂CO₃ and a superstoichiometric amount (200 mol%) of Zn (Scheme 3b; conditions B), where 3aq was obtained in 7% yield. This reductive annulation reaction was applicable to other arylalkylacetylenes and diphenylacetylene, affording the corresponding 4-chromanone derivatives 5ar–5at. The exclusive regioselectivity observed with the arylalkylacetylenes is notable in comparison with imperfect regioselectivities observed in the Rh⁴– and Rh⁵-catalyzed
reactions using such alkenes.$^{[2c,3]}$ It should also be noted that the reaction of silylacetylene 2a under conditions B did not produce the corresponding 4-chromanone at all, but afforded only 3aa.

In order to gain insight into the reaction pathways of the dehydrogenative and reductive annulation reactions, we performed deuterium-labeling experiments (Scheme 4). The reaction of SA deuterated at the formyl carbon ([D]-1a) and 2a under the conditions A afforded the expected product 3aa and 2-hydroxybenzyl alcohol with almost complete deuterium labeling of the benzylic position ([D]-4a), demonstrating the transfer of the deuterium atom of [D]-1a to another molecule of [D]-1a (Scheme 4a). The reaction of [D]-1a and 2q under the conditions B also afforded [D]-4a, while no deuterium incorporation into the annulation product 5aq was observed (Scheme 4b). Furthermore, the reductive annulation of 1a and 2q in the presence of D$_2$O resulted in substantial deuterium incorporation into both the 2- and 3-positions of 5aq (Scheme 4c). The latter two observations exclude a hydroacylation–oxy-Michael addition cascade, which may operate under Rh$^\text{III}$-catalyzed conditions (cf. Scheme 1a),$^{[2b,c]}$ as a mechanism for the reductive annulation.

On the basis of the above observations, we are tempted to propose possible catalytic cycles A and B for the dehydrogenative and the reductive annulation reactions, respectively (Scheme 5). In the catalytic cycle A, a Co$^\text{III}$ species generated by the reduction of the CoBr$_2$–dcpe precatalyst and 1a form a Co$^\text{II}$–aryloxide I, which then undergoes intramolecular aldehyde C–H oxidative addition to produce an acyl(hydrido)cobalt(III) species II. Unlike the Rh$^\text{III}$-catalyzed hydroacylation using SA,$^{[21]}$ the species II does not directly react with any alkenes. Instead, II undergoes insertion of another molecule of 1a into the Co–H bond to give an acyl(benzylxoy)cobalt(III) species III. Migratory insertion of the alkene 2a into the cobalt(III)–acyl bond of III is followed by C–O reductive elimination to furnish the product 3aa along with a Co$^\text{II}$–benzoxylide V. The reaction of V with 1a finally affords 2-hydroxybenzyl alcohol as the coproduct and thus complete a catalytic turnover.

The major difference of the catalytic cycle B from the cycle A is the involvement of Zn as a stoichiometric reductant. While the cycle B shares the key species I–III with the cycle A, the Co$^\text{III}$ species III is reduced by Zn into an acylcobalt(I) species VI bearing a zinc alkoxide moiety. Subsequent migratory insertion of 2q into the cobalt(I)–acyl bond and protonation of the resulting alkynylcobalt(I) species VII with 1a afford an α,β-unsaturated ketone VIII while regenerating the species I. Note that these reduction, migratory insertion, and protonation steps may take place in different orders (Schemes S1 and S2 in the Supporting Information), while we consider that the alkyn-dependent reaction outcomes can be better explained by the proposed mechanistic model. The zinc alkoxide moiety of VIII then undergoes intramolecular oxy-Michael addition. The resulting zinc enolate IX would be protonated by a coexisting proton source such as 1a or adventitious water to give the product 5aq along with zinc alkoxide species such as X, which would make
the reaction mixture basic. Note that the basic nature of the reaction mixture of reductive annulation was supported by electrophilic trapping experiments using benzyl bromide (see the Supporting Information).

We speculate that the unique reaction pathway of the present Co\(^{II}\)-catalysis compared with the Rh\(^{III}\)-catalyzed alkyne hydroacylation may be ascribed to more polarized nature of the Co\(^{III}\)–H bond than of a Rh\(^{III}\)–H bond\(^{[16]}\). Thus, the Co\(^{III}\)–H moiety of the intermediate II would serve as a better hydride donor to the C=O bond of 1a, thus opening the reaction channel to the acyl(benzyloxy)cobalt(III) intermediate III.

Scheme 5. Proposed catalytic cycles for the dehydrogenative and the reductive annulation reactions.

Besides the mechanistically distinct features compared with the Rh\(^{III}\)-catalyzed hydroacylation of SA, the present Co\(^{II}\)-catalysis would be complementary to the Rh\(^{III}\)-catalyzed dehydrogenative annulation (Scheme 1a) particularly for the accessibility to a variety of silyl-substituted chromones (Scheme 2). The product 3aa can be converted to various chromone-containing derivatives by way of facile iododesilylation with ICl (Scheme 6). Thus, the iodochromone intermediate 6 is amenable to a series of Pd-catalyzed C–C coupling reactions including Sonogashira coupling, cyclocarbonylation\(^{[17]}\), and annulation with benzyne\(^{[18]}\), thus affording the corresponding products 7–9, respectively, in good yields.

Scheme 6. Transformations of the silyl-substituted chromone 3aa.

In summary, we have identified unique reaction manifolds of a Co\(^{II}\)-diphosphine catalyst in the coupling of SA and internal alkynes\(^{[19,20]}\). Unlike the conventional Rh-catalyzed hydroacylation using the same reactants, the Co\(^{II}\) catalyst effects dehydrogenative or reductive annulation through C–H oxidative addition followed by C=O hydrometalation as common key steps to afford chromone or 4-chromanone derivatives, respectively.
The product selectivity primarily depends on the alkyne substrates, while its origin remains unclear at this time. Further studies on the Co-catalyzed reactions through aldehyde C–H activation are underway.

Acknowledgements

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Keywords: cobalt • C–H functionalization • alkynes • aldehydes • heterocycles

References


[15] Preliminary attempts to use other carbonyl compounds, such as those examined in the following work, as external hydrogen acceptors have not been successful: A. M. Whittaker, V. M. Dong, Angew. Chem., Int. Ed. 2015, 54, 1312-1315.
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