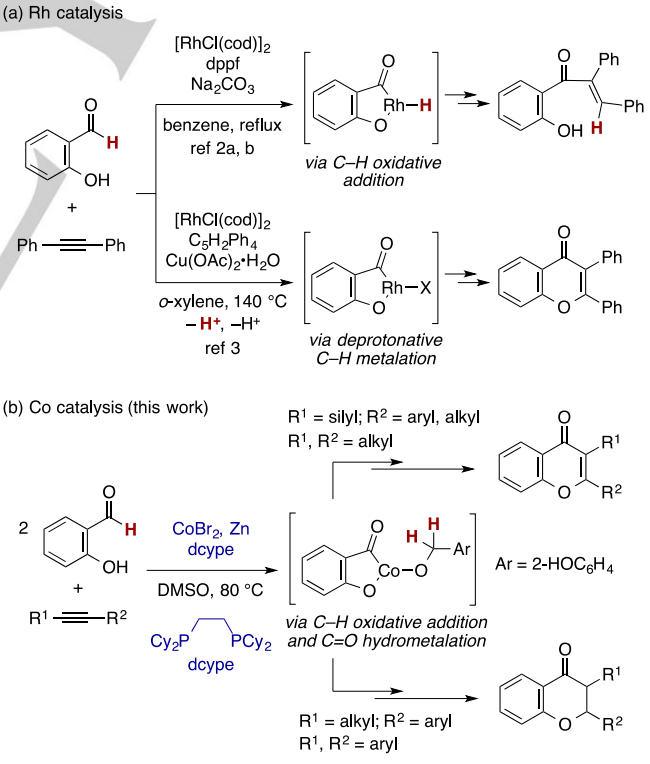
Cobalt-Catalyzed Annulation of Salicylaldehydes and Alkynes to Form Chromones and 4-Chromanones**

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 common key steps. The reductive annulation to 4-chromanones also involves the action of Zn as a stoichiometric reductant. Besides these mechanistic features, the present Co^{I} catalysis is complementary to the Rh^{I}- and Rh^{III}-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.[1] Such reactions often employ chelating aldehydes to facilitate the C–H activation and to prevent decarbonylation of the resulting acylmetal 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 arylcarbonyl motifs in natural products and bioactive substances. Indeed, hydroacylation and related acylation reactions of SA have been developed using alkynes,[2-5] alkenes,[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^{I} or Rh^{III} 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^{III} catalyst, in the presence of a Cu^{II} oxidant, effects oxidative annulation through deprotonative C–H metalation, alkyne insertion into Rh–C, and C–O reductive elimination to afford a chromone derivative.[3]

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.[9,10] We have also developed another Co^{I}–diphosphine catalyst as an alternative to the Wilkinson catalyst for the intermolecular olefin hydroacylation using a chelating aldimine.[11-13] 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^{I}–dcype (1,2-bis(dicyclohexylphosphino)ethane) catalytic systems promote annulation 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 annulation 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^{III} 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.

With the parallelism of Co^{I} and Rh^{I} catalysts in previous hydroacylation reactions in mind, we initially intended to achieve hydroacylation reaction using SA (**1a**) and an alkyne such as 1-phenyl-2-trimethylsilylacetylene (**2a**) using a Co^{I} catalyst. Contrary to this initial intention, we did not observe the expected

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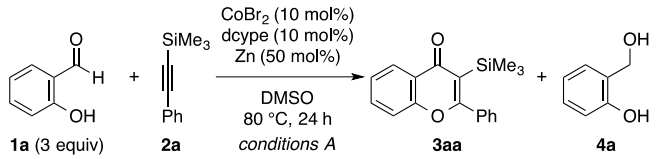
hydroacylation product in any of our screening experiments. Instead, a catalyst generated from $CoBr_2$ (10 mol%), dcype (10 mol%), and Zn (50 mol%) promoted the reaction of excess **1a** (0.3 mmol) and **2a** (0.1 mmol) in DMSO at 80 °C (conditions A), affording a chromone derivative **3aa** in 82% 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 reductant 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).

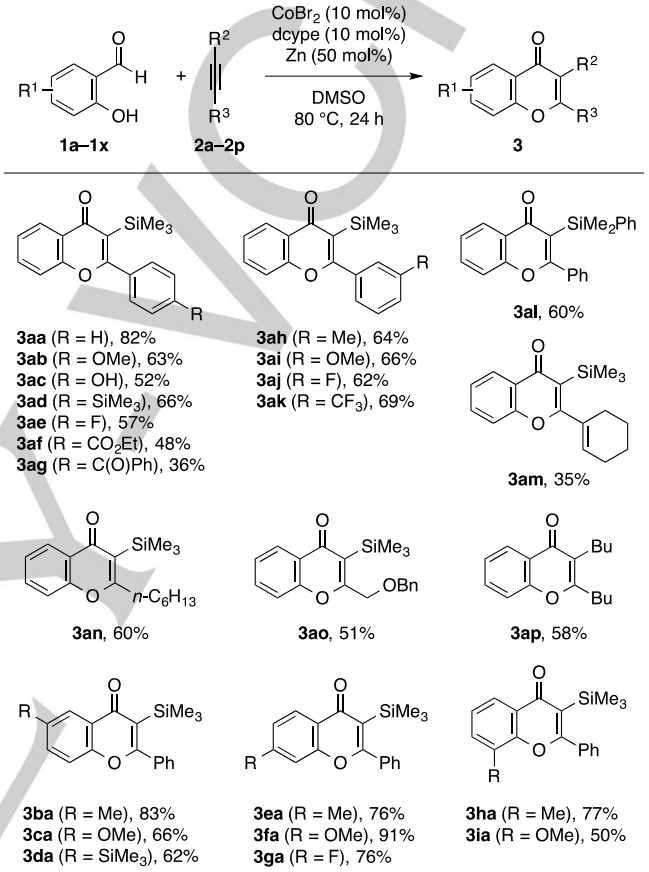
Table 1. Effect of reaction conditions on dehydrogenative annulation of salicylaldehyde (**1a**) and alkyne **2a**.[a]



Entry	Deviation from conditions A[b]	Yield of **3aa** [%][c]
1	none	82
2	dppe instead of dcype	11
3	dppp instead of dcype	6
4	dppf instead of dcype	0
5	dippf instead of dcype	0
6[d]	PCy_3 instead of dcype	0
7	Mn instead of Zn	41
8	In instead of Zn	16
9	THF instead of DMSO	8
10	MeCN instead of DMSO	0

[a] The reaction was performed on a 0.1 mmol scale. [b] Abbreviations: dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; dppf = 1,1'-bis(diphenylphosphino)ferrrocene; dippf = 1,1'-bis(diisopropylphosphino)ferrocene. [c] Determined by GC using *n*-tridecane as an internal standard. [d] 20 mol% of PCy_3 was used.

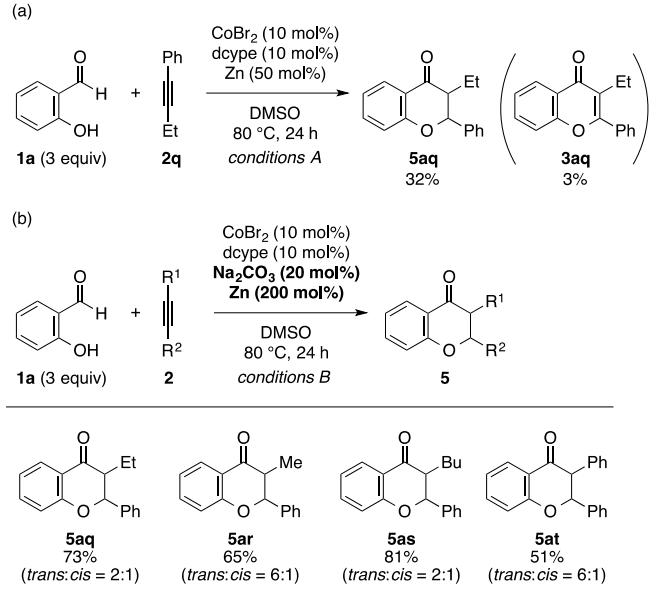
With the Co–dcype catalytic system in hand, we explored the scope of the dehydrogenative annulation (Scheme 2). A variety of 1-aryl-2-silylacetylenes participated in the reaction with **1a** to regioselectively afford the corresponding 2-aryl-3-silylchromones **3aa**–**3al**, with tolerance of functional 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 chromone 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**–**3ia** 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).



Scheme 2. Scope of the dehydrogenative annulation reaction of salicylaldehydes with silylacetylenes and dialkylacetylenes (0.3 mmol scale).

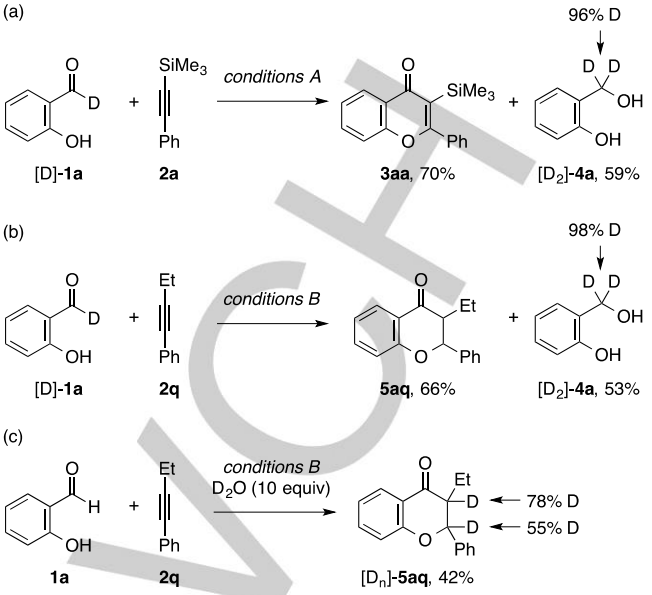
During exploration of the scope of alkynes in the dehydrogenative annulation, we found that the reaction of **1a** and 1-phenyl-1-propyne (**2q**) under the conditions A regioselectively produced a 4-chromanone derivative **5aq** in a modest yield of 32% with only a trace amount of the expected chromone 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 Na_2CO_3 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 Rh^{I}- and Rh^{III}-catalyzed

reactions using such alkynes.[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**.



Scheme 3. Reductive annulation of salicylaldehyde with arylalkylacetylene and diarylacetylene

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 deuteration of the benzylic position ([D_2]-**4a**), demonstrating the transfer of the aldehydic 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_2]-**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_2O 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 operates under Rh^I-catalyzed conditions (cf. Scheme 1a),[2b,c] as a mechanism for the reductive annulation.



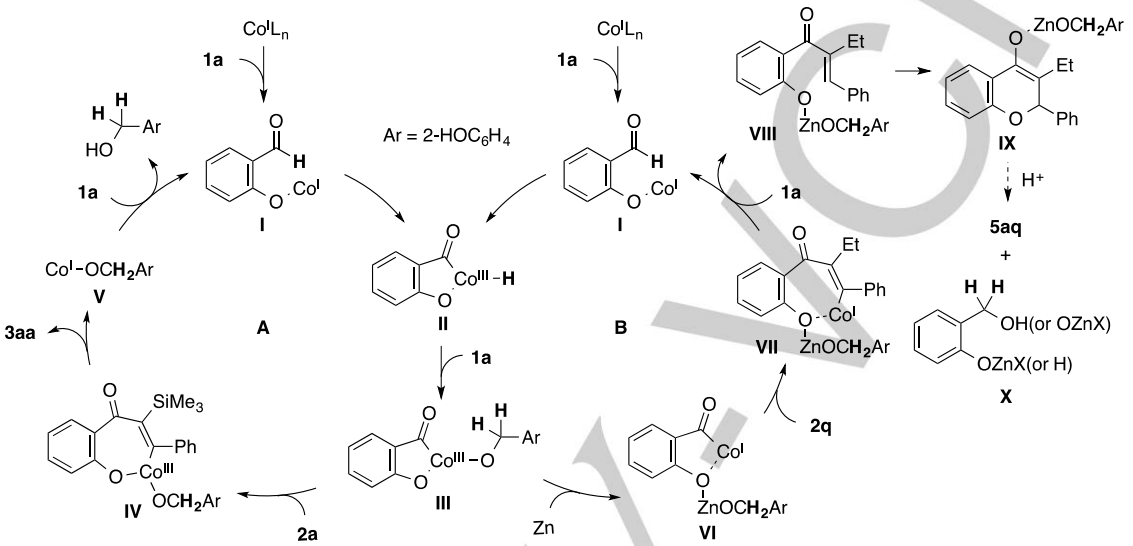
Scheme 4. Deuterium-labeling experiments.

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^I species generated by the reduction of the $CoBr_2$–dcype precatalyst and **1a** form a Co^I–aryloxide **I**, which then undergoes intramolecular aldehyde C–H oxidative addition to produce an acyl(hydrido)cobalt(III) species **II**. Unlike the Rh^I-catalyzed hydroacylation using SA,[2] the species **II** does not directly react with any alkynes. Instead, **II** undergoes insertion of another molecule of **1a** into the Co–H bond to give an acyl(benzyloxy)cobalt(III) species **III**. Migratory insertion of the alkyne **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^I–benzyloxide **V**. The reaction of **V** with **1a** finally afford 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^{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 alkenylcobalt(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 alkyne-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

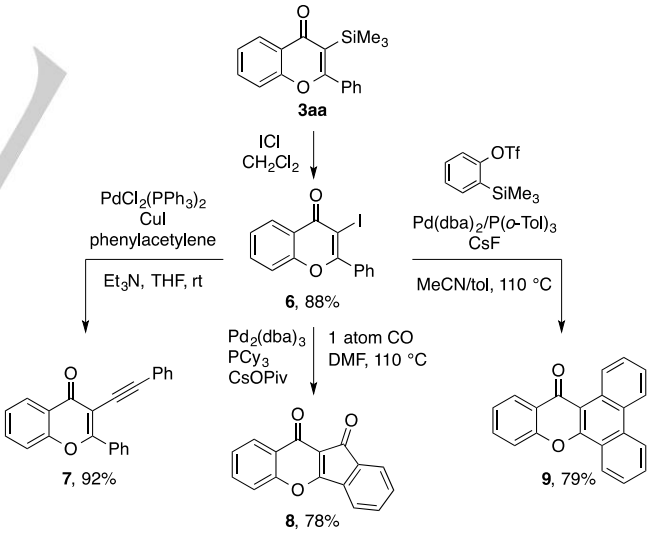
the reaction mixture basic. Note that the basic nature of the reaction mixture of reductive annulation was supported by electrophilic trapping experiments using benzyl bromide (see the Supporting Information).

We speculate that the unique reaction pathway of the present Co^{I} catalysis compared with the Rh^{I}-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^{I}-catalyzed hydroacylation of SA, the present Co^{I} 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^{I}–diphosphine catalyst in the coupling of SA and internal alkynes.[19,20] Unlike the conventional Rh^{I}-catalyzed hydroacylation using the same reactants, the Co^{I} 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 substituents, while its origin remains unclear at this time. Further studies on the Co^{I}-catalyzed reactions through aldehyde C–H activation are underway.

Acknowledgements

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

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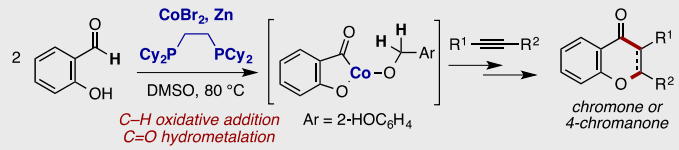

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Page No. – Page No.

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