Cobalt Catalysis

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

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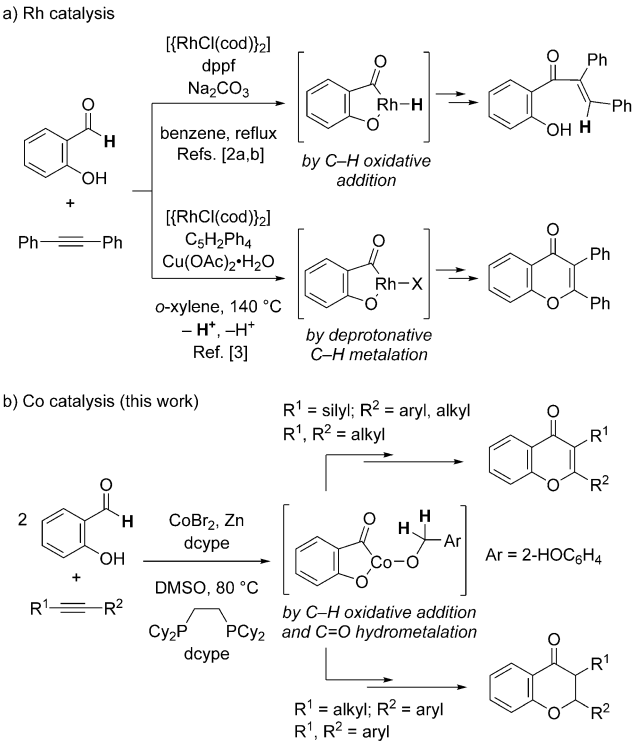
Abstract: *A unique cobalt(I)–diphosphine catalytic system has been identified for the coupling of salicylaldehyde (SA) and an internal alkyne affording a dehydrogenative annulation product (chromone) or a reductive annulation product (4-chromanone) depending on the alkyne substituents. Distinct from 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. In addition to these mechanistic features, the Co^{I} catalysis described herein 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 by means of transition-metal-mediated aldehyde C–H activation is 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 acyl metal species. Among various chelating aldehydes, salicylaldehyde (SA) is particularly attractive because of its ready availability as well as 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. For example, Miura and co-workers demonstrated two distinct reaction manifolds for the coupling of SA and an internal alkyne under Rh^{I} or Rh^{III} catalysis (Scheme 1 a). A Rh^{I} diphosphine catalyst promotes a standard hydroacylation process through C–H oxidative addition, alkyne insertion into the Rh–H bond, 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} species as oxidant, effects oxidative annulation through deprotonative C–H metalation, alkyne insertion into the Rh–C bond, and C–O reductive elimination to afford a chromone derivative.[3]



Scheme 1. Transition-metal-catalyzed reactions of salicylaldehyde and alkyne.

We have found that cobalt(I)–diphosphine catalysts can serve as viable alternatives to rhodium(I)–diphosphine catalysts for the intramolecular hydroacylation of 2-acylbenzaldehydes and 2-alkenylbenzaldehydes.[9,10] We have also developed another cobalt(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 cobalt(I)–dcype catalytic systems (dcype = 1,2-bis(dicyclohexylphosphino)ethane) promote annulation reactions of SA and internal alkynes to afford chromone or 4-chromanone derivatives depending on the alkyne substituents (Scheme 1 b). 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 reaction involves the action of Zn as a stoichiometric reductant. In addition to these mechanistically distinct features in comparison to Rh^{I} catalysis, the Co^{I} catalysis is complementary to the Rh^{III} catalysis as

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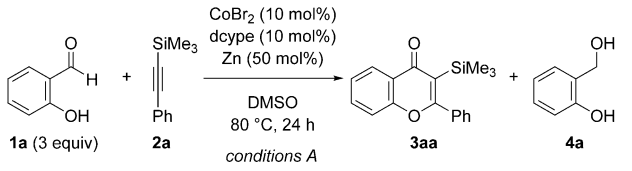
a method for the synthesis of chromones, which represent core structures of flavonoids, isoflavonoids, and related bioactive compounds.[14]

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

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

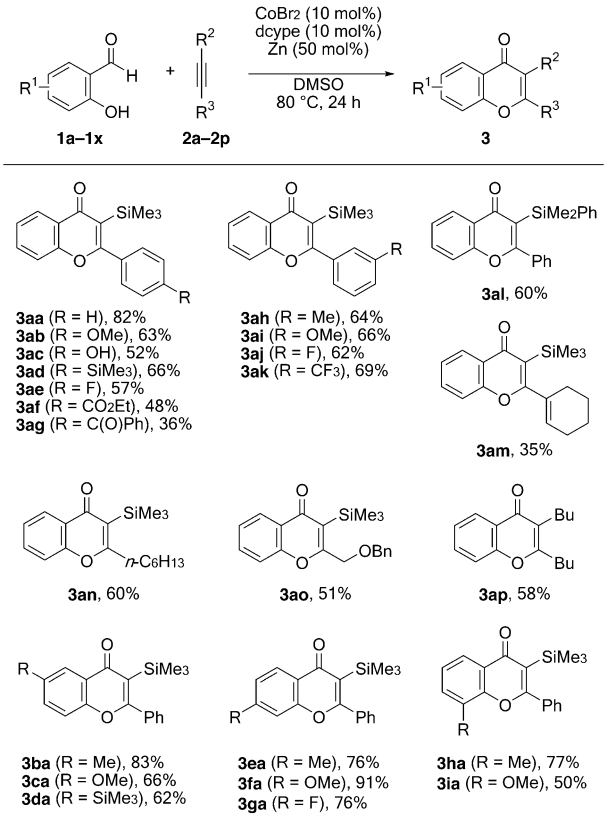


Entry	Deviation from conditions A[b]	Yield of **3aa** [%][c]
1	none	82
2	dppe instead of dcype	11
3	dppp instead of dcype	6
4	dppf instead of dcype	0
5	dippf instead of dcype	0
6[d]	PCy_3 instead of dcype	0
7	Mn instead of Zn	41
8	In instead of Zn	16
9	THF instead of DMSO	8
10	MeCN instead of DMSO	0

[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.

product **4a** apparently indicated that **1a** acted not only as a reactant but also as a hydrogen acceptor (see below), 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 significantly 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 7,8). The reaction became sluggish in other solvents, such as THF and MeCN (Table 1, entries 9,10).

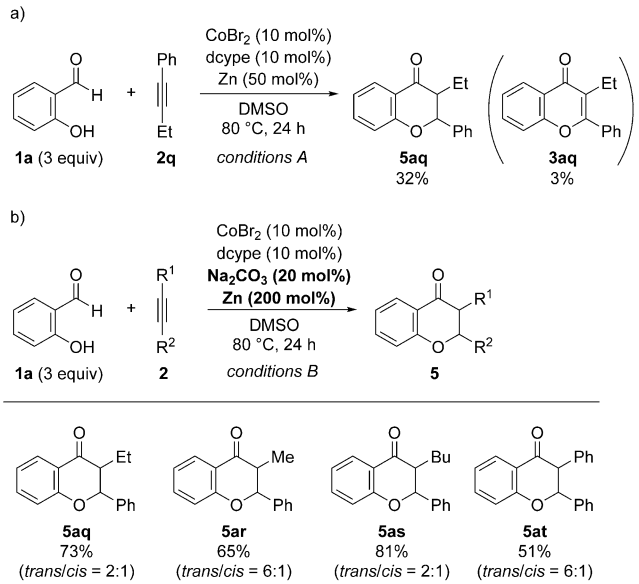
With the Co–dcype catalytic system in hand, we explored the scope of the dehydrogenative annulation (Scheme 2). A variety of 1-aryl-2-silylacetylenes participated in the reaction with **1a** to regioselectively afford the corresponding 2-aryl-3-silylchromones **3aa**–**3al**, with tolerance of functional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



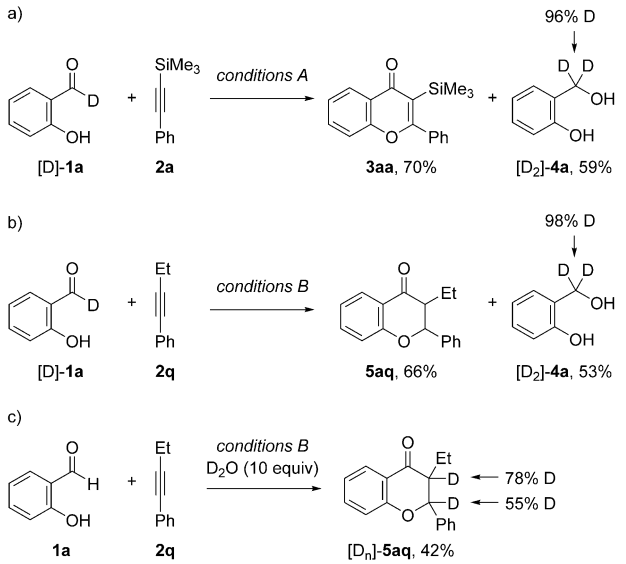
Scheme 2. Scope of the dehydrogenative annulation reaction of salicylaldehydes with silylacetylenes and dialkylacetylenes (0.3 mmol scale).

In addition to the 1-aryl-2-silylacetylenes, silylacetylenes bearing alkenyl and alkyl groups also underwent regioselective dehydrogenative annulation to afford the chromone derivatives **3am**–**3ao**. The catalytic system could also be applied 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. In contrast, 6-methoxysalicylaldehyde failed to participate in the dehydrogenative annulation with **2a**, presumably as a result of steric repulsion between the methoxy and the formyl groups, which would interfere with the formation of a metallacycle intermediate (see below).

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 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 of Na_2CO_3 (20 mol%) and a superstoichiometric amount of Zn (200 mol%; 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 detected with the arylalkylacetylenes is nota-



Scheme 3. Reductive annulation of salicylaldehyde with arylalkylacetylene and diarylacetylene.



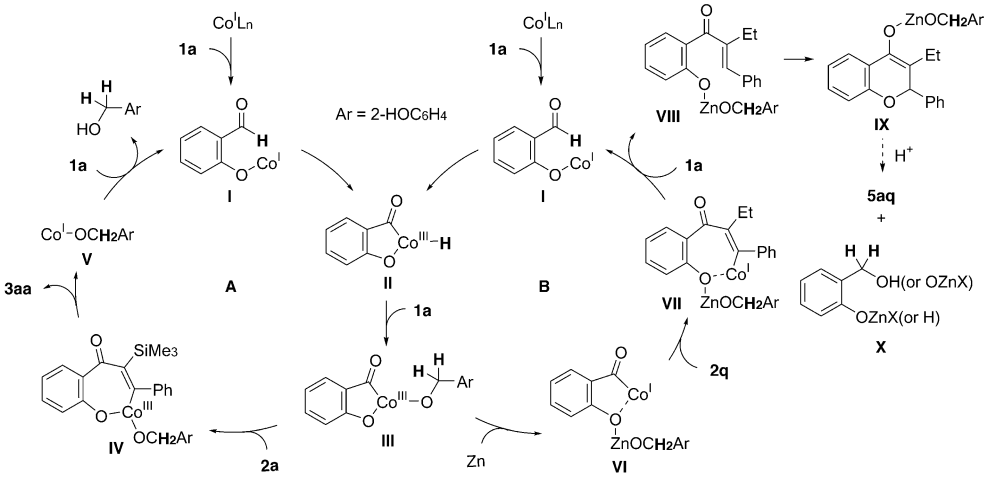
Scheme 4. Deuterium-labeling experiments.

ble in comparison with imperfect regioselectivities detected 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**.

To gain insight into the reaction pathways of the dehydrogenative and reductive annulation reactions, we performed deuterium-labeling experiments (Scheme 4). The reaction between SA deuterated at the formyl carbon ([D]-**1a**) and **2a** under conditions A afforded the expected product **3aa** as well as the 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 conditions B also afforded [D_2]-**4a**, while no deuterium incorporation into the annulation product **5aq** was detected (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 results exclude a hydroacylation–oxy-Michael addition cascade, which may operate under Rh^{I}-catalyzed conditions (see Scheme 1a),[2b,c] as a mechanism for the reductive annulation.

On the basis of the above results, we tentatively propose possible catalytic cycles A and B for the dehydrogenative and the reductive annulation reactions, respectively (Scheme 5). In catalytic cycle A, a Co^{I} species generated by reduction of the $CoBr_2$–dcype precatalyst and **1a** form a cobalt(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] 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 cobalt(I)–benzyloxide **V**. The reaction of **V** with **1a** finally affords 2-hydroxybenzyl alcohol as the coproduct and thus completes a catalytic turnover.

The major difference between catalytic cycle B from cycle A is the involvement of Zn as a stoichiometric reduc-

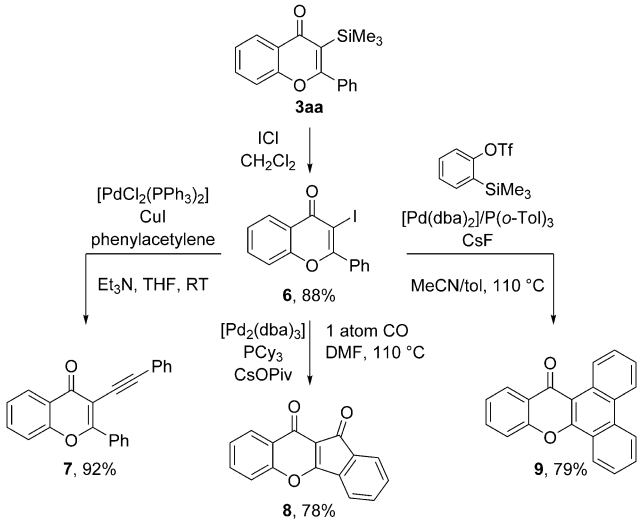


Scheme 5. Proposed catalytic cycles for the dehydrogenative and reductive annulation reactions.

tant. While cycle B shares the key species **I**–**III** with cycle A, 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 (see Schemes S1 and S2 in the Supporting Information), although 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 Co^{I} catalysis detailed herein compared with the Rh^{I}-catalyzed alkyne hydroacylation may be ascribed to the more polarized nature of the Co^{III}–H bond than of a Rh^{III}–H bond.[16] Thus, the Co^{III}–H moiety of 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**.

In addition to the mechanistically distinct features compared with the Rh^{I}-catalyzed hydroacylation of SA, the present Co^{I} catalysis would be complementary to Rh^{III}-catalyzed dehydrogenative annulation (Scheme 1a), particularly for accessibility to a variety of silyl-substituted chromones (Scheme 2). Product **3aa** can be converted into various chromone-containing derivatives by 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**. tol = toluene.

In summary, we have investigated the use of a unique cobalt(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 to afford chromone or 4-chromanone derivatives, respectively. The product selectivity primarily depends on the alkyne substituents, although its origin remains unclear at this time. Further studies on Co^{I}-catalyzed reactions through aldehyde C–H activation are underway.

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Keywords: aldehydes · alkynes · C-H functionalization · cobalt · heterocycles

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