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Rh-Catalyzed domino synthesis of 4-hydroxy-3-methylcoumarins *via* branch-selective hydroacylation†‡

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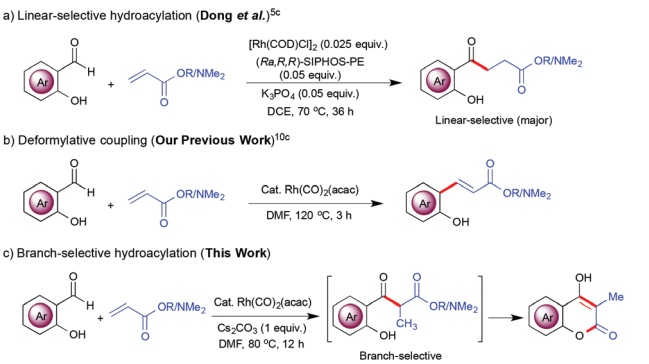
A Rh-catalyzed domino synthesis of 4-hydroxy-3-methylcoumarins *via* branch-selective hydroacylation of acrylates and acrylamides using salicylaldehydes is described. This protocol under phosphine-free Rh-catalyzed conditions provided 4-hydroxy-3-methylcoumarins in high yields with excellent functional group tolerance and high selectivity.

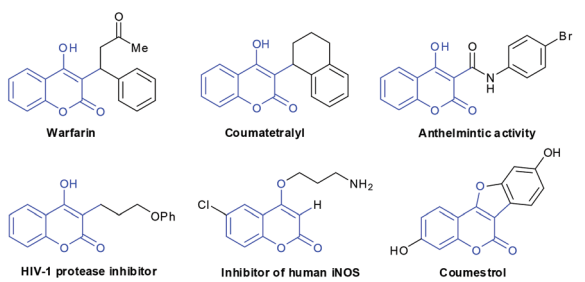
Introduction

In recent years, rhodium-catalyzed hydroacylation reactions with excellent atom-economy have played a major role in organic synthesis.[1–3] The introduction of a chelating group adjacent to the aldehyde has made the intermolecular hydroacylation process very successful by reducing the competitive decarbonylation pathway.[1,2] However, a few reactions have also been reported under rhodium-catalyzed conditions with non-chelated aldehydes.[3] In the present context, aldehydes featuring N,[4] O,[5] P[6] and S[7] chelating groups are known with promising reactivity in the olefin hydroacylation process. Dong *et al.* have reported Rh(I)-catalyzed coupling of salicylaldehydes with acrylates and acrylamides to generate hydroacylation products with modest to excellent linear-selectivities (Scheme 1a).[5c] Recently, Yang *et al.* have achieved the hydroacylation of *para*-quinone methides with salicylaldehydes to form α,α-diaryl-2-hydroxy acetophenones.[5d] However, branch-selectivity was achieved by additional co-ordination of olefin, nitrile, sulphide, phosphinite and with other catalytic systems.[8,9] In particular, Zhang and Bolm have reported the branch-selective hydroacylation of salicylaldehydes with enamides.[9g] Our group has been exploring the reactivity of salicylaldehyde under Rh-catalyzed conditions and developed (i) a method for the arylation of the C–H bond of aldehydes[10a] and (ii) a decarbonylative coupling process (Scheme 1b).[10b,c] Herein, we disclose the highly branch-selective hydroacylation of acrylates and acrylamides using salicylaldehydes under phosphine-free Rh-catalysis in the base-mediated tandem preparation of 4-hydroxy-3-methylcoumarins in high yields (Scheme 1c).

4-Hydroxycoumarins[11] are present in numerous natural products[11b] with varied biological applications such as anticoagulant,[12] anthelmintic,[13] antioxidant and antitumor[14] activities. Some of these molecules are shown in Scheme 2.



Scheme 1 Salicylaldehydes under Rh-catalysis.



Scheme 2 Biologically important molecules with a 4-hydroxycoumarin scaffold.

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†Dedicated to Professor Vinod K. Singh, IIT Kanpur on the occasion of his 60th birthday.

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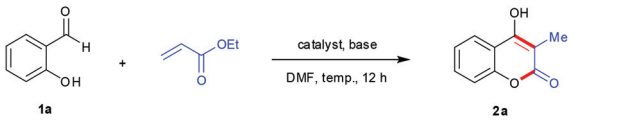
Results and discussion

In continuation of our earlier efforts, we explored the hydroacylation of acrylates with salicylaldehydes. It was initially studied with ethyl acrylate and salicylaldehyde (**1a**) under different reaction conditions (Table 1) to evolve a standardized protocol for the envisioned process. Interestingly, this led to hitherto unprecedented branch-selective hydroacylation and tandem cyclization to generate 4-hydroxy-3-methylcoumarin (**2a**) in 62% yield (entry 1). Furthermore screening other catalysts did not improve the yield (entries 2–4). However, the temperature variation studies (entries 5 and 6) had a positive effect and **2a** was isolated in 89% yield at 120 °C (entry 6). Bases other than Na_2CO_3 were less effective as they gave **2a** in lower yields (entries 7–10). Finally, a control reaction revealed the necessity of the Rh-catalyst for the process (entry 11). This screening thus provided a protocol with Na_2CO_3 in DMF at 120 °C and 12 h as the best conditions.

Furthermore, the efficiency of different alkyl acrylates was investigated as shown in Scheme 3. This study revealed better reactivity of ethyl acrylate in comparison with other alkyl acrylates by delivering the products in high yields. This reaction with 3 mmol scale of **1a** and 3 mol% lowered catalyst loading in the presence of ethyl acrylate afforded **2a** in 67% yield.

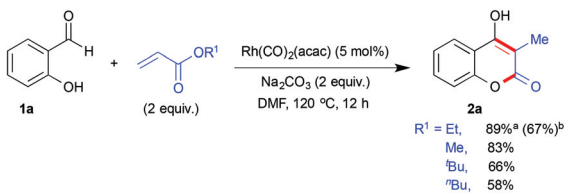
To expand the scope of this work, we next examined the reactivity of functionalized salicylaldehydes with ethyl acrylate and the results are given in Table 2. The reaction conditions offered high tolerance to halogens and the variation of the electronic properties of salicylaldehydes. For example, electron-rich salicylaldehydes with methyl and methoxy groups participated very well to give the corresponding coumarins **2b** and **2c** in 62% and 69% yields, respectively. Salicylaldehydes functionalized with halogens such as fluorine, chlorine and bromine reacted well to give the corresponding halogenated products **2d–2h** in 52–74% yields. Furthermore, the effect of sterics in salicylaldehydes was investigated by functionalization of the ring with the methoxy group. These substrates afforded products **2i** and **2j** in 76% and 82% yields, respectively. Under this protocol, 2-hydroxy-1-naphthaldehyde also participated well to give the coumarin product **2k** in 57% yield. Electron-deficient salicylaldehydes with acetyl, cyano, methoxycarbonyl and nitro groups as the ring substituents gave the corresponding products **2l–2o** in 61–80% yields. It should be noted that salicylaldehydes with free carbaldehyde and hydroxyl groups were well tolerated with high selectivity as the corresponding coumarin products **2p** and **2q** were formed in 77% and 60% yields. The overall branch-selectivity and functional group tolerance derived with our protocol is truly significant. This notably facilitated the tandem preparation of various functionalized 4-hydroxy-3-methylcoumarin products in good to high yields.

Table 1 Screening conditions[a]



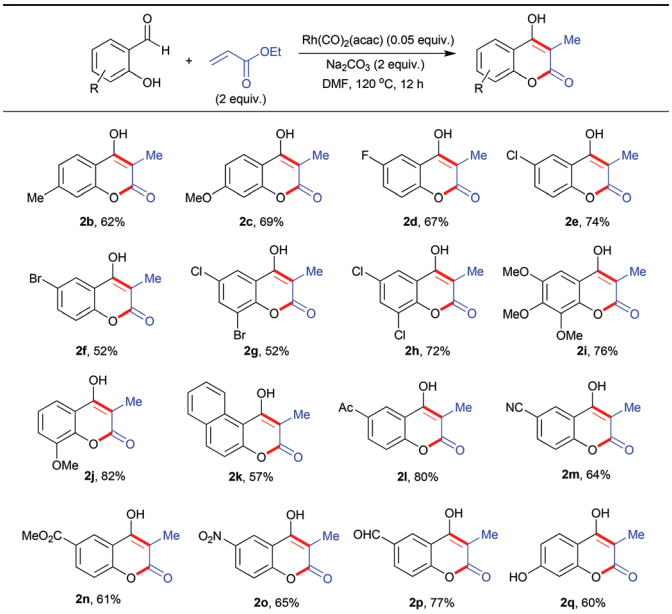
Entry	Catalyst	Base	Temp. (°C)	Yield **2a** (%)
1	$Rh(CO)_2(acac)$	Na_2CO_3	100	62
2	$RhCl_3/2PPh_3$	Na_2CO_3	100	25
3	$RhCl(CO)(PPh_3)_2$	Na_2CO_3	100	43
4	$RhCl(PPh_3)_3$	Na_2CO_3	100	53
5	$Rh(CO)_2(acac)$	Na_2CO_3	80	34
6	**$Rh(CO)_2(acac)$**	**Na_2CO_3**	**120**	**89**
7	$Rh(CO)_2(acac)$	$NaHCO_3$	120	83
8	$Rh(CO)_2(acac)$	K_2CO_3	120	76
9	$Rh(CO)_2(acac)$	KOAc	120	41
10	$Rh(CO)_2(acac)$	NaOAc	120	29
11	—	Na_2CO_3	120	—

[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv.), ethyl acrylate (1 mmol, 2 equiv.), catalyst (0.025 mmol, 0.05 equiv.), base (1 mmol, 2 equiv.), DMF, temp., 12 h.



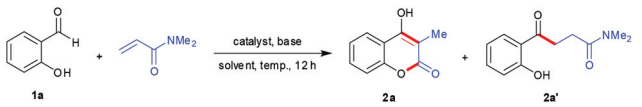
Scheme 3 Scope of alkyl acrylates. [a]General reaction conditions: **1a** (0.5 mmol, 1 equiv.), acrylate (1 mmol, 2 equiv.), $Rh(CO)_2(acac)$ (0.025 mmol, 0.05 equiv.), Na_2CO_3 (1 mmol, 2 equiv.), DMF (2 mL), 120 °C, 12 h. [b]With **1a** (3 mmol, 1 equiv.), ethyl acrylate (6 mmol, 2 equiv.), $Rh(CO)_2(acac)$ (0.09 mmol, 0.03 equiv.), Na_2CO_3 (6 mmol, 2 equiv.), DMF (10 mL), 120 °C, 12 h.

Table 2 Scope of functionalized salicylaldehydes with ethyl acrylate[a]



[a] Reaction conditions: functionalized salicylaldehyde (0.5 mmol, 1 equiv.), ethyl acrylate (1 mmol, 2 equiv.), $Rh(CO)_2(acac)$ (0.025 mmol, 0.05 equiv.), Na_2CO_3 (1 mmol, 2 equiv.), DMF (2 mL), 120 °C, 12 h.

Table 3 Screening conditions[a]



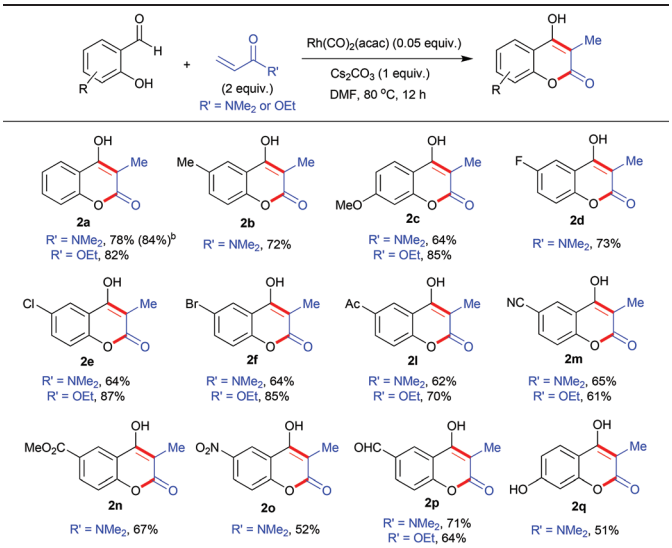
Entry	Catalyst	Base (equiv.)	Solvent	Temp. (°C)	Yield (%) **2a** (**2a′**)
1	$Rh(CO)_2(acac)$	Na_2CO_3 (2)	DMF	120	32 (6)
2	$Rh(CO)_2(acac)$	K_2CO_3 (2)	DMF	120	61
3	$Rh(CO)_2(acac)$	K_3PO_4 (2)	DMF	120	57 (13)
4	$Rh(CO)_2(acac)$	Cs_2CO_3 (2)	DMF	120	70 (4)
5	$Rh(CO)_2(acac)$	Cs_2CO_3 (1)	DMF	120	73 (5)
6	$Rh(CO)_2(acac)$	Cs_2CO_3 (1)	DMF	100	74 (4)
7	**$Rh(CO)_2(acac)$**	**Cs_2CO_3 (1)**	**DMF**	**80**	**78 (2)**
8	$RhCl_3/2PPh_3$	Cs_2CO_3 (1)	DMF	80	21
9	$RhCl(CO)(PPh_3)_2$	Cs_2CO_3 (1)	DMF	80	12
10	$RhCl(PPh_3)_3$	Cs_2CO_3 (1)	DMF	80	62 (2)
11	$Rh(CO)_2(acac)$	Cs_2CO_3 (1)	DMA	80	75 (5)
12	$Rh(CO)_2(acac)$	Cs_2CO_3 (1)	NMP	80	66 (4)
13	$Rh(CO)_2(acac)$	Cs_2CO_3 (1)	DCE	80	4 (28)
14	—	Cs_2CO_3 (1)	DMF	80	—

[a] Reaction conditions: **1a** (0.5 mmol, 1 equiv.), *N*,*N*-dimethylacrylamide (1 mmol, 2 equiv.), catalyst (0.025 mmol, 0.05 equiv.), base, solvent, temp., 12 h.

Furthermore, we have also studied the reactivity of *N*,*N*-dimethylacrylamide in this reaction (Table 3). Under the above established protocol conditions but with the *N*,*N*-dimethylacrylamide reactant, the coupling reaction with salicylaldehyde afforded 4-hydroxy-3-methylcoumarin (**2a**) in 32% yield along with a small amount of the linear hydroacylation product **2a′** (Table 3, entry 1). Screening of different bases indicated Cs_2CO_3 as a better choice of base (entry 4) over K_2CO_3 and K_3PO_4 (entries 2 and 3). With Cs_2CO_3 as the base the reaction furnished **2a** in 70% yield (entry 4). Furthermore fine tuning by decreasing the amount of base (entry 5) and the reaction temperature led to a higher yield of **2a** (entries 6 and 7). Thus the protocol involving Cs_2CO_3 (1 equiv.) in DMF at 80 °C afforded **2a** in 78% yield with a negligible amount of the side product (entry 7). Furthermore screening different rhodium catalysts led to inferior reactivity (entries 8–10). Different solvents investigated for their suitability including DMA, NMP and DCE offered mixed results (entries 11–13) and were inferior to that obtained with the DMF solvent (entry 7). A control reaction without the rhodium catalyst did not provide the coumarin product (entry 14). Overall, the above investigation showed that the conditions with Cs_2CO_3 (1 equiv.) in DMF at 80 °C are the best choice to obtain high product yields (entry 7) and these conditions were employed in our further study.

The scope of the reaction was further investigated using *N*,*N*-dimethylacrylamide in combination with different functionalized salicylaldehydes (Table 4). The substitution of electron-rich and electron-deficient groups in salicylaldehyde was well tolerated to give the corresponding functionalized 4-hydroxy-3-methylcoumarin products (**2a–2f** and **2l–2q**) in good to excellent yields. This reaction with 4 mmol scale of **1a** and 3 mol% lowered catalyst loading in the presence of *N*,*N*-di-

Table 4 Scope of salicylaldehydes with *N*,*N*-dimethylacrylamide/ethyl acrylate[a]



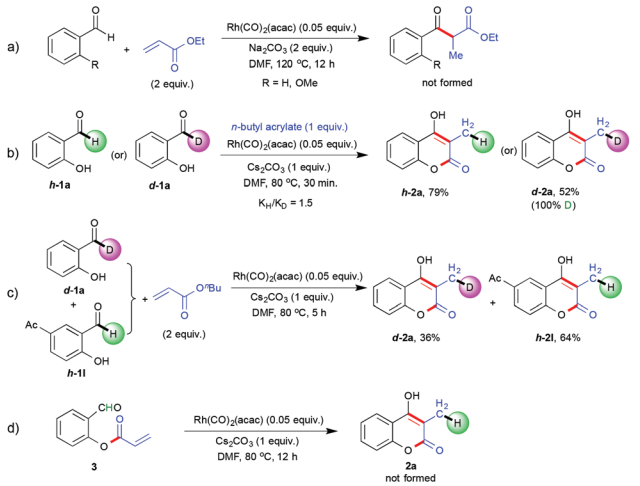
[a] Reaction conditions: **1a** or functionalized salicylaldehyde (0.5 mmol, 1 equiv.), *N*,*N*-dimethylacrylamide/ethyl acrylate (1 mmol, 2 equiv.), $Rh(CO)_2(acac)$ (0.025 mmol, 0.05 equiv.), Cs_2CO_3 (0.5 mmol, 1 equiv.), DMF (2 mL), 80 °C, 12 h. [b] With **1a** (4 mmol, 1 equiv.), *N*,*N*-dimethylacrylamide (8 mmol, 2 equiv.), $Rh(CO)_2(acac)$ (0.12 mmol, 0.03 equiv.), Cs_2CO_3 (4 mmol, 1 equiv.), DMF (10 mL), 80 °C, 12 h.

methylacrylamide also afforded **2a** in 84% yield. In particular, salicylaldehydes with fluoro, chloro and bromo substituents reacted normally and furnished the corresponding halo functionalized 4-hydroxy-3-methylcoumarins (**2d–2f**) in reasonably good yields. The reaction of 4-hydroxyisophthalaldehyde also furnished **2p** as the sole product in 71% yield. This example demonstrates the highly selective reactivity of the vicinal hydroxy aldehyde function in the salicylaldehyde. The broadness of the protocol was demonstrated with *N*,*N*-dimethylacrylamide and functionalized salicylaldehydes containing fluoro, chloro, bromo, acetyl, cyano and carbaldehyde groups. These reactions afforded the corresponding 4-hydroxy-3-methylcoumarins in good yields.

To check the generality of the reaction conditions, we next examined the reactivity of functionalized salicylaldehydes with ethyl acrylate under these conditions. Interestingly, this protocol also offered general reactivity with ethyl acrylate to give the corresponding 4-hydroxy-3-methylcoumarins (**2a**, **2c**, **2e**, **2f**, **2l**, **2m** and **2p**) in good to high yields.

To gain mechanistic insight into the reaction, simple benzaldehyde and 2-methoxybenzaldehyde were allowed to react with ethyl acrylate under the optimized conditions. In this case, unreacted benzaldehyde was recovered (Scheme 4a). This demonstrated the necessity of the *ortho*-hydroxy group for the reaction to proceed to give the product.

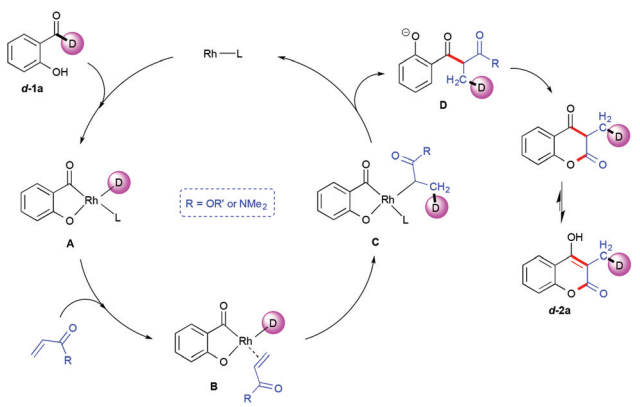
Two parallel reactions were conducted with *n*-butyl acrylate in combination with salicylaldehyde (*h*-**1a**) and its deuterium derivative (*d*-**1a**) (Scheme 4b) under the optimized conditions. This delivered the corresponding coumarin products *h*-**2a** and



Scheme 4 Control experiments.

d-**2a** in 79% and 52% yields with the coumarin product *d*-**2a** showing 100% deuterium incorporation. The calculated K_H/K_D of 1.5 indicated that the oxidative addition step is not the rate determining step and the reductive elimination step is expected to be the turnover limiting step.[15] Furthermore, a cross-over experiment carried out between the deuterium-labeled salicylaldehyde-d_1 (*d*-**1a**) and 5-acetyl salicylaldehyde (*h*-**1l**) did not show any deuterium scrambling between the substrates (Scheme 4c). Furthermore the possibility of the intramolecular hydroacylation process was investigated using the salicylaldehyde derivative **3** (Scheme 4d) and product **2a** was not obtained. This effectively ruled out the intramolecular pathway.

From the above control experiments and literature reports,[5c,8b] a mechanistic proposal is depicted in Scheme 5 for the branch-selective hydroacylation of salicylaldehyde and tandem formation of 4-hydroxy-3-methylcoumarin (*d*-**2a**). The rhodacycle **A** is generated by oxidative insertion of rhodium into the C–H bond of the aldehyde. This is followed by olefin co-ordination to give complex **B** which in turn involves branch-selective hydride insertion to form complex **C**. This further undergoes reductive elimination to generate the branched product **D** along with the regeneration of the rhodium catalyst. Product **D** undergoes base-mediated intramolecular trans-esterification to form 4-hydroxy-3-methylcoumarin (*d*-**2a**).[16] Selective formation of intermediate **C** leading to branch-selectivity is probably due to the influence of ligand on rhodium and such a selectivity was earlier reported in the literature under varied ligand conditions.[8a,9a]



Scheme 5 Proposed mechanistic cycle.

Conclusions

In summary, we have described efficient catalytic protocols for the synthesis of 4-hydroxy-3-methylcoumarins involving branch-selective hydroacylation of acrylates and acrylamides using salicylaldehydes. The rhodium protocol with Na_2CO_3 was proved to be effective for reactions with acrylates, while the protocol with Cs_2CO_3 showed efficient reactivity both with acrylates and acrylamides. The high branch-selectivity coupled with efficient functional group tolerance enabled the pot-economical direct synthesis of several functionalized 4-hydroxy-3-methylcoumarins in high yields.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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