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One-Pot Synthesis of Oxo Acid Derivatives by Rh^{I}-Catalyzed Chelation-Assisted Hydroacylation

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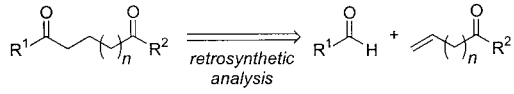
Various oxo acid derivatives were obtained directly from the reaction of aliphatic and aromatic aldehydes with ω-alkenoic acid derivatives in the presence of rhodium(I) complexes and 2-amino-3-picoline.

γ-Oxo acid derivatives are an important class of compounds that serve as intermediates for various heterocyclic compounds such as lactones, β-lactam antibiotics and isoquinolines.[1] But the synthetic scheme is not simple, because retrosynthetic analysis shows that the umpoled synthon or masked form of the acyl group should be used. Therefore, many indirect forms of synthetic protocols have been developed using nitroalkane,[2] diazo compounds,[3] etc.[4] One simple way to solve this problem is intermolecular hydroacylation: the direct synthesis of ketones from aldehydes with alkenes[5] or alkynes[6] through C–H bond activation by a transition metal catalyst. These types of catalytic C–H bond activation have been focused on by many synthetic organic chemists because they are one of the best ways of avoiding many environmental problems that can occur with industrial organic synthesis.[7] Willis et al. utilized functionalized olefins such as acrylic acid derivatives for the hydroacylation with β-alkoxy or β-sulfanyl aldehydes,[8] and for the hydroimination with aldimines as an umpoled synthon, producing γ-oxo acid derivatives after hydrolysis of the resulting ketimine.[9] Since we have also developed a direct synthesis of ketones from common aldehydes,[10] we were intrigued to use our chelation-assistant strategy for the synthesis of γ-oxo acid derivatives, and to extend the use of alkyl ω-alkenoate producing oxo esters that have different tether lengths.[11]

In this paper, we wish to report a general direct synthesis of various oxo acid derivatives from aldehydes and alkenoic acid derivatives (Scheme 1).

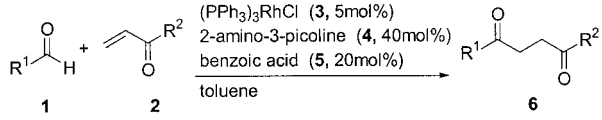


n = 0, 1, 2; R^1= Aromatic, Aliphatic; R^2= OR, NR_2

Scheme 1. Retrosynthetic analysis of various oxo acid derivative.

In our experiment, when the reaction of benzaldehyde (**1a**) and methyl acrylate (**2a**) was carried out at 130 °C for 1 h under the cocatalysis of $RhCl(PPh_3)_3$ (**3**, 5 mol-%), 2-amino-3-picoline (**4**, 40 mol-%), and benzoic acid (**5**, 20 mol-%), γ-oxo ester **6a** was isolated in a 96% yield exclusively (Table 1, Entry 1).

Table 1. Chelation-assisted hydroacylation of aldehyde **1** with functionalized olefin **2**.



1 **2** **6**

Entry	Aldehyde	Olefin	Temp./ time	Product **6**
	R^1 (**1**)	R^2 (**2**)[a]		yield [%][b]
1	Ph (**1a**)	MeO (**2a**)	130 °C/1 h	**6a**, 96 (100)
2	4-MeC_6H_4 (**1b**)	(**2a**)	130 °C/1 h	**6b**, 94 (100)
3	Ph (**1a**)	*t*BuO (**2b**)	130 °C/1 h	**6c**, 96 (100)
4	Ph (**1a**)	EtO (**2c**)	130 °C/1 h	**6d**, 91 (96)
5	4-BrC_6H_4 (**1c**)	MeO (**2a**)	130 °C/2 h	**6e**, 83 (85)
6	4-$CF_3C_6H_4$ (**1d**)	(**2a**)	130 °C/4 h	**6f**, 88 (94)
7	4-NCC_6H_4 (**1e**)	(**2a**)	150 °C/6 h	**6g**, 69 (73)
8	Ph (**1a**)	Me_2N (**2d**)	150 °C/6 h	**6h**, 75 (100)
9	*n*C_5H_{11} (**1f**)	EtO (**2c**)	150 °C/6 h	**6i**, 91 (98)
10	Cy (**1g**)	(**2c**)	150 °C/6 h	**6j**, 81 (94)
11	*t*C_4H_9 (**1h**)	(**2c**)	150 °C/6 h	**6k**, 0 (0)[c]

[a] 2 equiv. of **2** (based on the aldehyde) were used. [b] Isolated yield. GC yields are given in parentheses. [c] Compound **12** was obtained in 64% GC yield.

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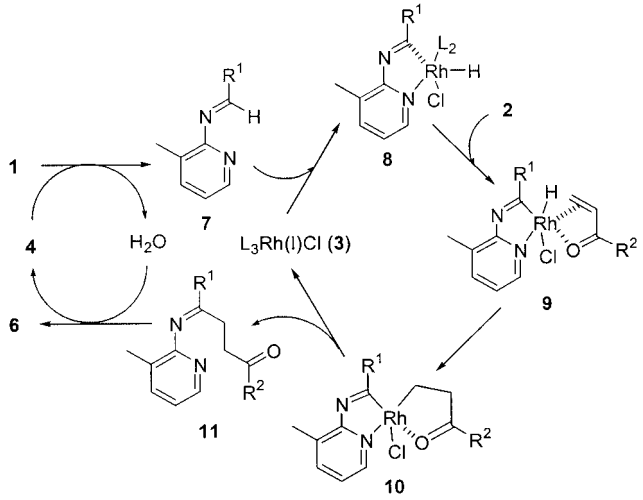
The reaction proceeded smoothly without any hydrolysis or condensation steps. Aldehyde **1b** bearing an electron-donating group shows a better reactivity than one having an electron-withdrawing group such as the trifluoromethyl group since the reaction of **1d** requires a longer reaction time (Entries 2 and 6).

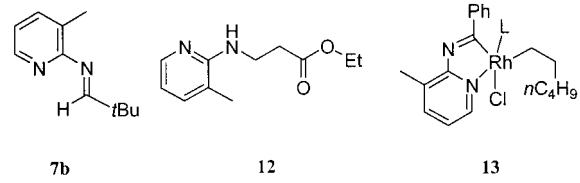
The other functional groups did not show any dramatic signs of interference in this hydroacylation reaction (Entries 3–5) except for nitrile **1e**, which required more vigorous conditions (Entry 7). In the case of acrylamide (**2d**), a moderate yield of the corresponding γ-oxo amide **6h** was isolated (Entry 8). Instead of aromatic aldehydes, aliphatic aldehydes such as **1f** and **1g** were also applied to this hydroacylation of acrylic ester, and fairly good yields of the expected γ-oxo esters were obtained for primary and secondary alkanals (Table 1, Entries 9–10).

The reaction mechanism can be inferred as shown in Scheme 2. Initially, aldehyde **1** reacts with 2-amino-3-picoline (**4**) to generate aldimine **7**, in which the C–H bond is cleaved by $RhCl(PPh_3)_3$ (**3**) to generate the iminorhodium(III) hydride **8**. Coordination of acrylic ester or amide **2** to **8** and the subsequent hydride insertion into **9** leads to complex **10**. Reductive elimination in **10** affords **11** and the rhodium catalyst **3**. Ketimine **11** is further hydrolyzed by H_2O, which was previously formed by condensation of **1** and **4**, producing a γ-oxo acid derivative **6** with the generation of **4**. Fortunately, a potential competitive side reaction, a 1,4-addition reaction of **2** with **4**, was not observed since **4** is more reactive towards aldehyde **1** than towards **2** generating **7** in situ. However, in the case of a tertiary alkanal such as **1h**, the expected **6k** was not obtained, but only 1,4-addition product **12** was isolated in 64% yield along with a 33% yield of aldimine **7b** based on **4** (Table 1, Entry 11). The reason must be that the C–H bond of **7b** is hardly cleaved by rhodium(I) of **3** due to the steric hindrance of the *tert*-butyl group in **7b**, which drives a 1,4-addition reaction of amine **4** to **2c**.



Scheme 2. Proposed mechanism for hydroacylation of **2** with **1** in the presence of **3** and **4**.

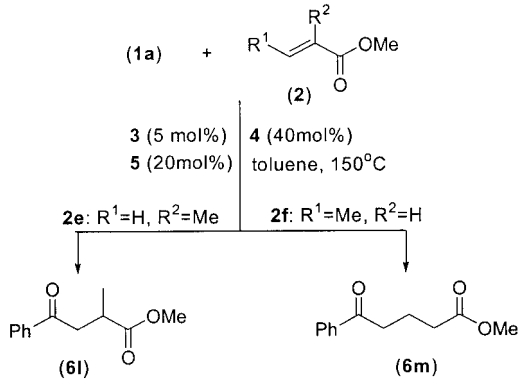
To compare the reactivity of acrylate **2a** (Table 1, Entry 1) with that of non-functionalized olefins, the reaction of



7b **12** **13**

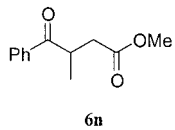
aldehyde **1a** with 1-hexene was performed at 130 °C for 1 h in the presence of an identical catalyst to give only a 29% isolated yield of heptanophenone.[12] The high efficiency of the reaction with methyl acrylate compared to 1-hexene is because with acrylate a stable five-membered metallacycle through carbonyl coordination[13] as well as a five-membered (imino)metallacycle like in complex **10** can be formed, while only a single metallacycle like in complex **13** is generated with 1-hexene. This implies that the rate-determining step of hydroacylation with acrylic ester or amide is hydrometallation in **9** forming **10**.

When the reaction of methyl 2-methyl acrylate (**2e**) and **1a** was carried out in the presence of an identical catalytic system, a corresponding branched alkyl γ-oxo ester **6l** was obtained (Scheme 3). But the reaction is so sluggish that 96 h are required to complete it. In contrast to **2e**, when the regioisomeric olefin, methyl 2-crotonate (**2f**), was used, linear alkylated δ-oxo ester **6m** was isolated without forming the branched alkylated γ-oxo ester **6n**.



Isolated Yield of **6l** (GC)	Reaction Time	Isolated Yield of **6m** (GC)
18% (27%)	24h	(9%)
55% (67%)	48h	71% (74%)
67% (77%)	72h	96% (100%)
91% (100%)	96h	

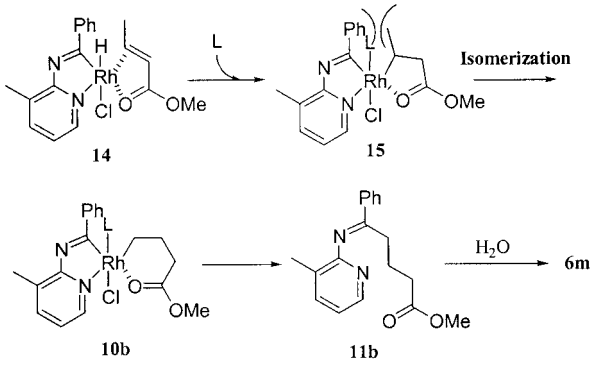
Scheme 3. Comparison of hydroacylation of **2e** and **2f** with **1a**.



6n

The reaction also needed a long reaction time, and was completed in 72 h. Initially, the hydrometallation of the Rh–H group into **2f** in **14** generates branched alkylrhodium complex **15** (Scheme 4). The steric congestion at the rhodium center in **15** allows the skeletal isomerization of the

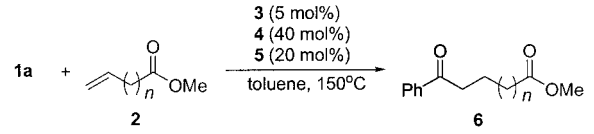
branched alkyl group to the sterically less congested linear alkylrhodium(III) complex **10b**. This type of isomerization can be seen in some transition metal catalyzed reactions.[14]



Scheme 4. Mechanism for the formation of **6m** from **1a** and **2f**.

Next, we extended our strategy to prepare oxo esters having a lengthy tether from ω-alkenoates; methyl 3-butenoate (**2g**) and methyl 4-pentenoate (**2h**) were applied to hydroacylation with benzaldehyde (Table 2). The reactions were facile and the required time for completing the reactions are as follows: 4 h for **2g**, 6 h for **2h**, and just 1.5 h for **2a** (Entries 1, 2, 3). For comparison, when the reactions of **2a**, **2g**, and **2h** were performed in the same reaction time (1.5 h), the corresponding δ-oxo ester **6m** and ε-oxo ester **6o** were isolated in a 59% and 49% yield, respectively, while a 92% isolated yield of **6a** was obtained with **2a** (Entries 1, 4, and 5). The highly reactive nature of **2a** compared with **2g** and **2h** can be explained by the fact that a stable five-membered metallacyclic complex **10** is formed with **2a** whereas stable metallacyclic intermediates seem not to be formed with **2g** and **2h**.

Table 2. Synthesis of γ-, δ-, and ε-oxo acid methyl esters from the reaction of **1a** with **2a**, **2g**, and **2h**.[a]



Entry	*n* (**2**)[b]	Reaction time	Product **6**	Yield [%][c]
1	0 (**2a**)	1.5 h	**6a**	92 (100)
2	1 (**2g**)	4 h	**6m**	96 (100)
3	2 (**2h**)	6 h	**6o**	93 (100)
4	1 (**2g**)	1.5 h	**6m**	59 (68)
5	2 (**2h**)	1.5 h	**6o**	49 (58)

[a] Reagents and conditions: $(PPh_3)_3RhCl$ (**3**, 5 mol-%), 2-amino-3-picoline (**4**, 40 mol-%), benzoic acid (**5**, 20 mol-%), toluene, 150 °C. [b] 2 equiv. of **2** (based on the aldehyde) were used. [c] Isolated yield. GC yields are given in parentheses.

In conclusion, a synthesis of various oxo acid derivatives has been achieved by direct chelation-assisted hydroacylation of ω-alkenoic acid derivatives with aromatic and aliphatic aldehydes. These olefins are even more reactive than those having no functional groups, probably due to the formation of a properly sized metallacyclic complex intermediate through carbonyl coordination. Further applications of these hydroacylation reactions with functionalized olefins are under study.

Experimental Section

Typical Procedures for Hydroacylation (Table 1, Entry1): A screw-capped pressure vial (1 mL) equipped with a magnetic stirring bar was charged with benzaldehyde (**1a**, 26.5 mg, 0.25 mmol), methyl acrylate (**2a**, 43 mg, 0.5 mmol), $(PPh_3)_3RhCl$ (**3**, 11.6 mg, 0.013 mmol), 2-amino-3-picoline (**4**, 10.8 mg, 0.1 mmol), benzoic acid (**5**, 6.1 mg, 0.05 mmol), and toluene (80 mg). The reaction mixture was stirred in an oil bath that was preheated at 130 °C for 1 h. After cooling to room temperature, the organic layer was extracted with diethyl ether, and dried with anhydrous $MgSO_4$ and purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 15:1) to afford 39.8 mg (96%) of methyl 4-oxo-4-phenylbutyrate (**6a**).

Supporting Information (see footnote on the first page of this article): General experiments, materials, typical procedures, and data including ^1H NMR, ^{13}C NMR, IR, HRMS, elemental analyses, and mass spectra.

Acknowledgments

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