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Direct Intermolecular Hydroacylation of *N*,*N*-Dialkylacrylamides with Aldehydes Catalyzed by a Cationic Rhodium(I)/dppb Complex

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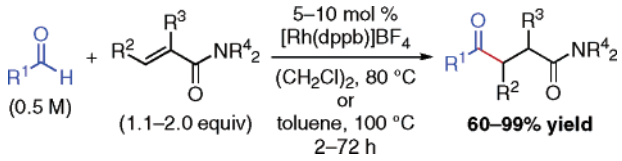
ABSTRACT



A cationic rhodium(I)/dppb complex catalyzed direct intermolecular hydroacylation of *N*,*N*-dialkylacrylamides with both aliphatic and aromatic aldehydes has been achieved through the stabilization of acylrhodium intermediates by alkene chelation to rhodium. This method represents a versatile new route to γ-ketoamides in view of the high atom economy and commercial availability of substrates.

Transition-metal-catalyzed intermolecular hydroacylation of alkenes and alkynes with aldehydes[1−7] is a highly atom-economical method[8] for the preparation of unsymmetrical ketones. Although rhodium catalysts are most frequently used for this transformation, facile decarbonylation from acylrhodium intermediates results in low product yield and low catalytic efficiency.[4] To suppress the undesired decarbonylation, several chelation-assisted strategies have been developed (Figure 1, **A**−**D**).[9−15] The pioneering work by Suggs demonstrated that C−H bond activation of 2-aminopicoline-derived aldimines furnishes nitrogen-stabilized intermediates **A**, which react with alkenes intermolecularly to give ketone

(1) For examples of Rh-catalyzed intramolecular hydroacylation of 4-alkenals, see: (a) Sakai, K.; Ide, J.; Nakamura, N. *Tetrahedron Lett.* **1972**, *13*, 1287. (b) Sakai, K. *J. Synth. Org. Chem. Jpn.* **1993**, *51*, 733. (c) Tanaka, M.; Sakai, K.; Suemune, H. *Curr. Org. Chem.* **2003**, *7*, 353. (d) Lochow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 1281. (e) Larock, R. C.; Oertle, K.; Potter, G. J. *J. Am. Chem. Soc.* **1980**, *102*, 190. (f) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936. (g) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667. (h) Morgan, J. P.; Kundu, K.; Doyle, M. P. *Chem. Commun.* **2005**, 3307. (i) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042.

(2) For examples of Rh-catalyzed intramolecular hydroacylation of 4-alkynals, see: (a) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492. (b) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296. (c) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 8078.

(3) For synthesis of larger cyclic compounds via Rh-catalyzed intramolecular hydroacylation, see: (a) Gable, K. P.; Benz, G. A. *Tetrahedron Lett.* **1991**, *32*, 3473. (b) Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610. (c) Sato, Y.; Oonishi, Y.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1218. (d) Oonishi, Y.; Taniuchi, A.; Mori, M.; Sato, Y. *Tetrahedron Lett.* **2006**, *47*, 5617. (e) Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031. (f) Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem.−Eur. J.* **2004**, *10*, 5681.

(4) For Rh-catalyzed intermolecular hydroacylation, see: (a) Scwartz, J.; Cannon, J. B. *J. Am. Chem. Soc.* **1974**, *96*, 4721. (b) Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* **1980**, *192*, 257. (c) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognio, J. M.; Dural, P. *J. Organomet. Chem.* **1982**, *240*, 285. (d) Vora, K. P. *Synth. Commun.* **1983**, *13*, 99. (e) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451.

(5) For Ru-catalyzed intermolecular hydroacylation, see: (a) Kondo, T.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *28*, 6229. (b) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286. (c) Kondo, T.; Hiraishi, N.; Morisaki, Y.; Wada, K.; Watanabe, Y.; Mitsudo, T.-A. *Organometallics* **1998**, *17*, 2131.

(6) For Ni-catalyzed intermolecular hydroacylation, see: Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554.

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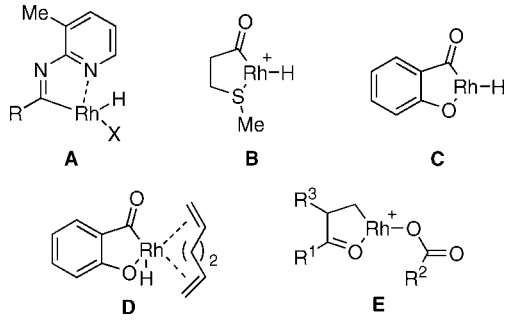
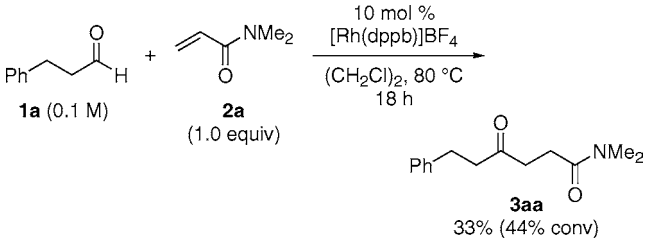


Figure 1. Isolated or proposed chelation-assisted hydroacylation intermediates **A**−**D** and proposed hydrogen-mediated coupling intermediate **E**.

products.[9] Jun et al. developed a number of efficient C−C bond-forming reactions by employing in situ formation of these 2-aminopicoline-derived aldimines.[10,11] Willis et al. developed a direct hydroacylation of alkenes and alkynes with a 3-methylsulfanyl-substituted aldehyde through the formation of sulfur-stabilized intermediate **B**.[12,13] Miura et al. developed a direct hydroacylation of alkynes with 2-hydroxybenzaldehyde through the formation of oxygen-stabilized intermediate **C**.[14] Tanaka, Suemune, and co-workers developed a direct hydroacylation of dienes with 2-hydroxybenzaldehyde.[15] They proposed that the reaction may proceed through double chelation stabilized intermediate **D**. Very recently, a novel intermolecular hydroacylation that does not require aldehyde chelation assistance was developed by Krische and co-workers.[16] Branch-selective intermolecular hydroacylation products were obtained by a hydrogen-mediated coupling of carboxylic anhydrides with styrenes and activated alkenes through the formation of cationic Rh-(III) intermediate **E** followed by hydrogenolytic cleavage of the rhodium−carbon bond, although the use of aliphatic carboxylic anhydrides lowered the yield of the hydroacylation products (Figure 1, **E**). In this Communication, we describe a cationic rhodium(I)/dppb complex catalyzed direct intermolecular hydroacylation of *N*,*N*-dialkylacrylamides with both aliphatic and aromatic aldehydes through the stabilization of acylrhodium intermediates by means of alkene chelation to rhodium instead of aldehyde chelation.

We recently reported a rhodium-catalyzed regio- and enantioselective intermolecular [4 + 2] carbocyclization of 4-alkynals with *N*,*N*-dialkylacrylamides.[17] In the course of that study, we observed the formation of an intermolecular hydroacylation byproduct in low yield.[18] We anticipated that the chelation of *N*,*N*-dialkylacrylamides to rhodium sufficiently stabilizes the acylrhodium intermediate, so the chelation of an alkyne moiety of 4-alkynals to rhodium may not be necessary. We were pleased to find that the reaction of hydrocinnamaldehyde (**1a**) with *N*,*N*-dimethylacrylamide (**2a**) at 0.1 M concentration in the presence of 10 mol % of [Rh(dppb)]BF_4 proceeded to give γ-ketoamide **3aa** in 33% yield at 44% conversion (Scheme 1).

Scheme 1



After screening various reaction conditions, we have determined that the yield of **3aa** highly depends on the choice of ligand and the concentration of **1a**. [Rh(dppe)]BF_4 and [Rh(dppf)]BF_4 showed low catalytic activities, and [Rh-(BINAP)]BF_4 and $RhCl(PPh_3)_3$ furnished no hydroacylation product. Employing a high concentration (0.5 M of **1a**) significantly accelerated the reaction. Thus, the reaction of **1a** with **2a** was conducted at 80 °C and 0.5 M concentration in the presence of 5 mol % of [Rh(dppb)]BF_4, which furnished γ-ketoamide **3aa** in 67% yield (Table 1, entry 1). A series of aliphatic aldehydes **1a**−**c** and *N*,*N*-dialkylacrylamides **2a**−**d** were subjected to the above optimal reaction conditions. 3-Methyl- and 2-methyl-substituted *N*,*N*-dialkylacrylamides **2b** and **2c** reacted with **1a** to give γ-ketoamides **3ab** and **3ac**, respectively, in excellent yield for short reaction times (entry 2, 95% yield, 2 h; entry 3, 97% yield, 5 h). However, *N*-methylmaleimide (**2d**) failed to react with **1a** (entry 4). The reactions of *n*-octanal (**1b**) and cyclohexanecarboxaldehyde (**1c**) with **2c** also proceeded to give the corresponding γ-ketoamides **3bc** and **3cc**, respectively, in excellent yields (entries 5 and 6).

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(13) Very recently, Willis et al. reported that coordination of the O atom of the hemilabile P−O−P ligand to rhodium increased the stability of the active catalyst. See: Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7618.

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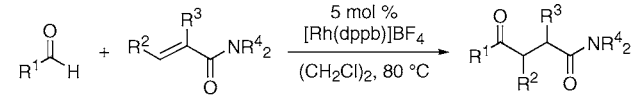
(16) Hong, Y.-T.; Barchuk, A.; Krische, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6885.

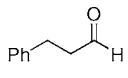
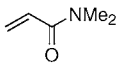
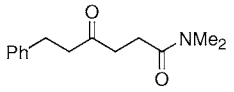
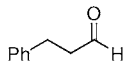
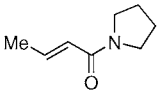
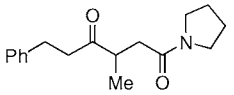
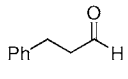
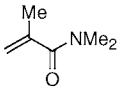
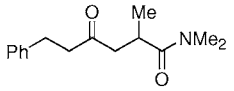
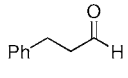
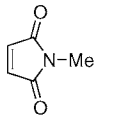
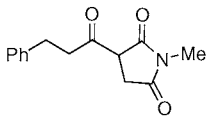
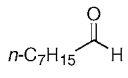
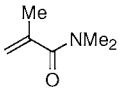
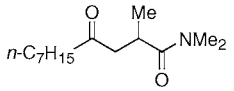
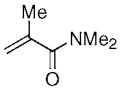
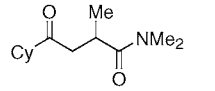
(17) Tanaka, K.; Hagiwara, Y.; Noguchi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7260.

(18) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Eur. J. Org. Chem.* **2006**, 3582.

Table 1. $Rh(I)^+$/dppb-Catalyzed Direct Intermolecular Hydroacylation of *N*,*N*-Dialkylacrylamides **2a**−**d** with Aliphatic Aldehydes **1a**−**c**[a]

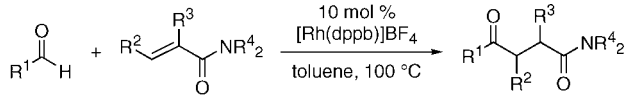


1 (0.5 M) **2** (1.1 equiv) **3**

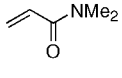
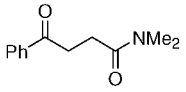
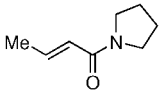
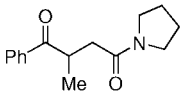
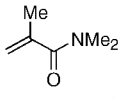
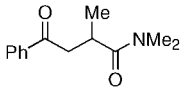
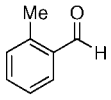
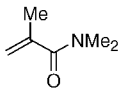
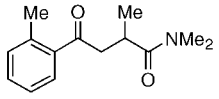
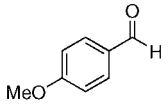
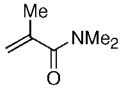
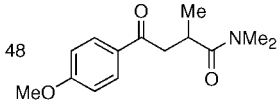
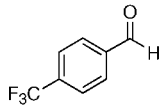
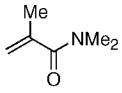
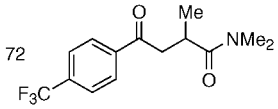
entry	aldehyde	alkene	time (h)	product (% yield[b])
1	 **1a**	 **2a**	42	 **3aa** (67)
2	 **1a**	 **2b**	2	 **3ab** (95)
3	 **1a**	 **2c**	5	 **3ac** (97)
4	 **1a**	 **2d**	18	 **3ad** (0)
5	 **1b**	 **2c**	5	 **3bc** (99)
6	 **1c**	 **2c**	14	 **3cc** (98)

[a] $[Rh(dppb)]BF_4$ (0.025 mmol), **1** (0.50 mmol), **2** (0.55 mmol), and $(CH_2Cl)_2$ (1.0 mL) were used. [b] Isolated yield.

Table 2. $Rh(I)^+$/dppb-Catalyzed Direct Intermolecular Hydroacylation of *N*,*N*-Dialkylacrylamides **2a**−**c** with Aromatic Aldehydes **1d**−**g**[a]



1 (0.5 M) **2** **3**

entry	aldehyde	alkene (equiv)	time (h)	product (% yield[b])
1	 **1d**	 **2a** (1.1 equiv)	72	 **3da** (60)
2	 **1d**	 **2b** (1.1 equiv)	72	 **3db** (75)
3	 **1d**	 **2c** (1.1 equiv)	22	 **3dc** (84)
4	 **1e**	 **2c** (2.0 equiv)	72	 **3ec** (92)
5	 **1f**	 **2c** (2.0 equiv)	48	 **3fc** (83)
6	 **1g**	 **2c** (2.0 equiv)	72	 **3gc** (72)

[a] $[Rh(dppb)]BF_4$ (0.050 mmol), **1** (0.50 mmol), **2** (0.55−1.00 mmol), and toluene (1.0 mL) were used. [b] Isolated yield.

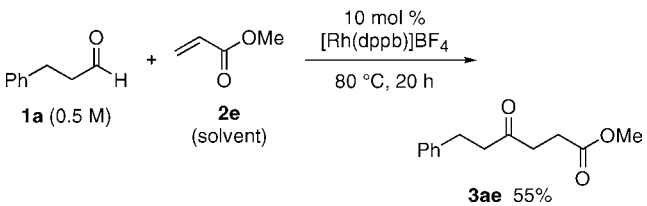
Not only aliphatic aldehydes **1a**−**c** but also benzaldehyde (**1d**) reacted with **2a**−**c** to give the corresponding γ-ketoamides in good to high yields (Table 2, entries 1−3), although the reactions required high catalyst loading (10 mol %) and high reaction temperature (100 °C). The steric and electronic effects were also investigated, which revealed that although the reactions of sterically demanding *o*-tolualdehyde (**1e**) and electron-rich 4-methoxybenzaldehyde (**1f**) with **2c** proceeded in high yields (entries 4 and 5), the reaction of electron-deficient 4-trifluoromethylbenzaldehyde (**1g**) with **2c** furnished the corresponding γ-ketoamide **3gc** in lower yield than that of benzaldehyde (**1d**) (entry 6).

The reaction of methyl acrylate (**2e**) was also investigated. Although the reaction of **1a** with 1.1 equiv of **2e** was inefficient, the use of **2e** as a solvent furnished the expected γ-ketoester **3ae** in 55% yield (Scheme 2).[19]

Because the reactions of aromatic aldehydes required a higher reaction temperature (100 °C) than those of aliphatic aldehydes (80 °C), chemoselective hydroacylation of an aliphatic aldehyde over an aromatic aldehyde was attempted. The reaction of 4-(3-oxopropyl)benzaldehyde (**4**), possessing both aliphatic and aromatic aldehyde moieties, with **2c** (1.1 equiv) in the presence of 5 mol % of $[Rh(dppb)]BF_4$ at 80 °C furnished monohydroacylation product **5** in 71% yield through the selective C−H bond activation of the aliphatic aldehyde moiety (Scheme 3).[20]

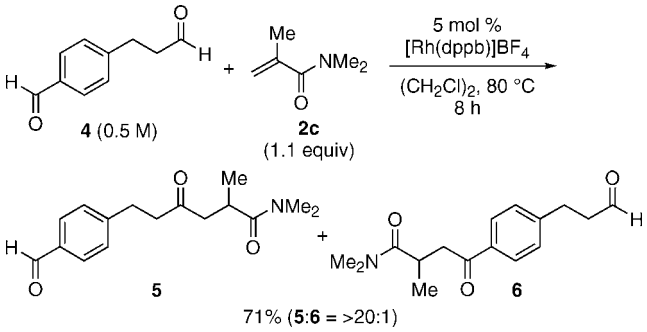
Scheme 4 shows a possible mechanism for the present intermolecular hydroacylation.[21] An oxidative addition of the

Scheme 2

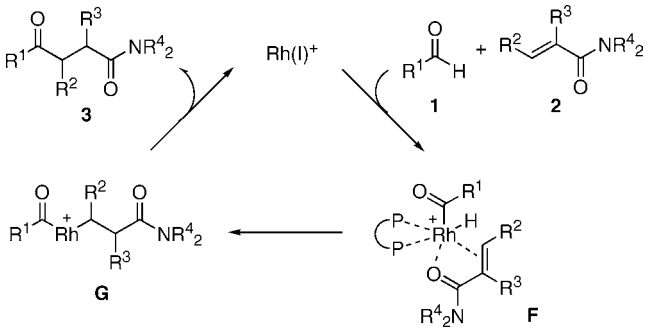


(19) A branched regioisomeric product (ca. 8% yield) was detected by ^1H NMR analysis of the crude reaction mixture.

Scheme 3



Scheme 4



aldehyde C−H bond to rhodium(I) affords rhodium acyl hydride **F**, which may be stabilized by the bidentate coordination of *N*,*N*-dialkylacrylamide **2**. Addition of the rhodium hydride to the alkene then provides acylrhodium intermediate **G**. Reductive elimination furnishes γ-ketoamide **3** and regenerates the Rh(I) catalyst. Consistent with this mechanism, the hydroacylation of methyl acrylate (**2e**), which has a lower coordinating ability than *N*,*N*-dialkylacrylamides **2a**−**c**, required a large excess of **2e** (Scheme 2). Furthermore, *N*-methylmaleimide (**2d**), which cannot coordinate to rhodium in a bidentate fashion, failed to react with aldehyde **1a** (Table 1, entry 4).

(20) A dihydroacylation product (ca. 10% yield) was detected by ^{1}H NMR analysis of the crude reaction mixture.

(21) Treatment of aldehyde **1a** or **1d** and *N*,*N*-dimethylmethacrylamide (**2c**) with dppb (5 mol %) at 80 °C for 5 h furnished no hydroacylation product. This result denies the possibility of a dppb-catalyzed Stetter reaction. For tributylphosphine-mediated Stetter reaction of arylaldehydes and *N*,*N*-dialkylacrylamides, see: Gong, J. H.; Im, Y. J.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2002**, *43*, 1247.

In conclusion, we have demonstrated that the cationic rhodium(I)/dppb complex catalyzed direct intermolecular hydroacylation of *N*,*N*-dialkylacrylamides with aldehydes represents a versatile new method for the synthesis of γ-ketoamides in view of the high atom economy and commercial availability of substrates. Asymmetric variants of this reaction and further utilization of the alkene chelation strategy are currently under investigation in our laboratory.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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