

# Highly Regioselective Intermolecular Hydroacylations of Enamides with Salicylaldehydes

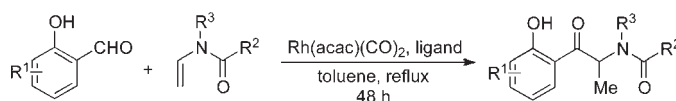
Hui-Jun Zhang and Carsten Bolm\*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1,  
D-52056 Aachen, Germany

carsten.bolm@oc.rwth-aachen.de

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## ABSTRACT



Highly regioselective intermolecular hydroacylations of enamides under rhodium catalysis with monodentate phosphane ligands are reported for the first time. The presence of MeCN facilitates this novel C–C bond formation, and the electron-deficient phosphine P(*p*-F-Ph)<sub>3</sub> has proven most effective for the direct hydroacylation of 1-vinyl-2-pyrrolidinone. Accordingly, an atom-economic synthetic route to  $\alpha$ -amido ketones from readily available substrates has been developed.

The transition metal-catalyzed hydroacylation of unsaturated hydrocarbons represents a powerful synthetic tool for the construction of new carbon–carbon bonds, and it has become an important example for efficient and atom-economic processes in organic synthesis.<sup>1</sup> Expanding the substrate scope proved challenging, particularly because of the occurrence and facileness of undesired decarbonylation reactions. So far, the reported examples mostly involve reactive electron-poor or strained olefins as unsaturated hydrocarbons, such as acrylate esters,<sup>2</sup> acrylamides,<sup>3</sup> 1,5-

hexadienes,<sup>4</sup> methylenecyclopropanes,<sup>5</sup> cyclopropenes,<sup>6</sup> or norbornenes.<sup>7,8</sup> In contrast, hydroacylation reactions of electron-rich olefins such as vinyl ethers and enamides have remained unknown. Here, we present for the first time a highly regioselective rhodium-catalyzed hydroacylation of enamides with salicylaldehydes as carbonyl components leading to a variety of  $\alpha$ -amido ketones.<sup>9</sup>

For the initial reactivity screening of various rhodium/ligand combinations (Table 1), we focused on the reaction between salicylaldehyde (**1a**) and 1-vinyl-2-pyrrolidinone (**2a**). First, cationic rhodium complex [Rh(dppb)]BF<sub>4</sub> [formed in situ from [Rh(ndb)<sub>2</sub>]BF<sub>4</sub> and dppb under

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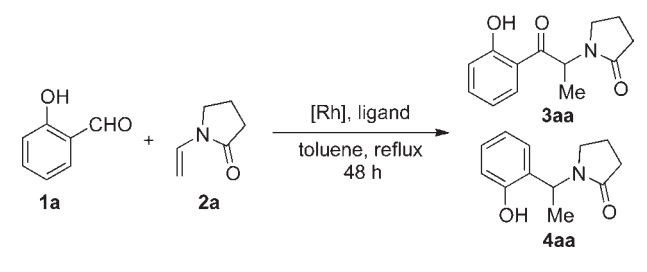
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**Table 1.** Optimization of the Rhodium-Catalyzed Reaction between Salicylaldehyde (**1a**) and 1-Vinyl-2-pyrrolidinone (**2a**)<sup>a</sup>



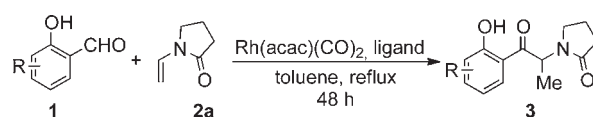
entry	[Rh]	[Rh] mol %	ligand	yield <sup>b</sup> of <b>3aa</b> (%)
1 <sup>c</sup>	Rh(nbd) <sub>2</sub> BF <sub>4</sub>	10	dppb	—
2	RhCl(PPh <sub>3</sub> ) <sub>3</sub>	10	—	trace
3 <sup>d</sup>	[Rh(cod)Cl] <sub>2</sub>	5	dppf	12 <sup>e</sup>
4	Rh(acac)(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub>	10	dppf	15 <sup>e</sup>
5	Rh(acac)(CO) <sub>2</sub>	20	<i>rac</i> -BINAP	21 <sup>e</sup>
6	Rh(acac)(CO) <sub>2</sub>	10	( <i>R</i> )-PhanePhos	48
7	Rh(acac)(CO) <sub>2</sub>	20	( <i>R</i> )-PhanePhos	62
8	Rh(acac)(CO) <sub>2</sub>	20	PPh <sub>3</sub>	66
9 <sup>f</sup>	Rh(acac)(CO) <sub>2</sub>	10	PPh <sub>3</sub>	64
10 <sup>g</sup>	Rh(acac)(CO) <sub>2</sub>	10	P( <i>p</i> -F-Ph) <sub>3</sub>	70
11 <sup>g</sup>	Rh(acac)(CO) <sub>2</sub>	20	P( <i>p</i> -F-Ph) <sub>3</sub>	90

<sup>a</sup> Standard conditions: [Rh] and ligand (ratio = 1:1) were stirred in toluene (0.3 mL) for 1 h at room temperature, and then **1a** (0.3 mmol) and **2a** (1.8 mmol) were added. The reaction mixture was heated to reflux for 48 h. <sup>b</sup> Based on **1a**. <sup>c</sup> H<sub>2</sub> was introduced to form [Rh(dppb)]BF<sub>4</sub>. <sup>d</sup> The addition of Na<sub>2</sub>CO<sub>3</sub> (10 mol %) was necessary. <sup>e</sup> Ratios of **3aa**:**4aa**: 1:0.4 (entry 3), 1:0.3 (entry 4), 1:0.1 (entry 5). <sup>f</sup> [Rh]:PPh<sub>3</sub> = 1:1.5; MeCN (6 equiv) was added. <sup>g</sup> [Rh]:P(*p*-F-Ph)<sub>3</sub> = 1:1.3.

hydrogen] was tested,<sup>3</sup> but no hydroacylation product was observed (Table 1, entry 1). In the presence of Wilkinson catalyst RhCl(PPh<sub>3</sub>)<sub>3</sub>,<sup>4</sup> only a trace amount of the expected product **3aa** was formed (entry 2). The combination of [Rh(cod)Cl]<sub>2</sub>, dppf, and Na<sub>2</sub>CO<sub>3</sub> catalyzed the hydroacylation, but the yield of **3aa** was only 12% (entry 3). In addition, decarbonylation product **4aa** was formed, and the ratio of **3aa**/**4aa** was 1:0.4. No base had to be added in hydroacylation reactions catalyzed by Rh(acac)(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub> and Rh(acac)(CO)<sub>2</sub> (entries 4–11). Those two complexes were combined with various mono- and bidentate phosphines, and the activities of the resulting in situ formed catalysts were studied. Of particular interest were phosphines, which previously had successfully been applied as ligands in hydroacylation reactions such as Chiraphos,<sup>10a,c</sup> *rac*-Binap,<sup>10a–c</sup> Me-DuPhos,<sup>10b–d</sup> dppf,<sup>10e,f</sup> dppb,<sup>3a</sup> DuanPhos,<sup>10g</sup> DPEphos,<sup>10h</sup> and Josiphos.<sup>6</sup> In the presence of Rh(acac)(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub> and dppf neither the yield of

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**Table 2.** Hydroacylations of Enamide **2a** with Salicylaldehydes **1b–h**<sup>a</sup>



entry	<b>1</b>	reaction conditions <sup>b</sup>	product	yield (%)
1		condition A condition B		73 85
2		condition A condition B		79 89
3		condition A condition B		70 69
4		condition A condition B		65 84
5		condition A condition B		49 60
6		condition A condition B		47 64
7		condition A condition B		80 78

<sup>a</sup> Rh(acac)(CO)<sub>2</sub> and ligand were stirred in toluene (0.3 mL) for 1 h at room temperature, and then **1** (0.3 mmol) and **2a** (1.8 mmol) were added. The reaction mixture was heated to reflux for 48 h. <sup>b</sup> Condition A: use of Rh(acac)(CO)<sub>2</sub> (10 mol %), PPh<sub>3</sub> (15 mol %), and MeCN (6 equiv). Condition B: use of Rh(acac)(CO)<sub>2</sub> (10 mol %) and P(*p*-F-Ph)<sub>3</sub> (13 mol %).

**3aa** nor the ratio of **3aa**/**4aa** was improved, and the results were similar to those obtained in the catalysis with [Rh(cod)Cl]<sub>2</sub>/dppf (Table 1, entry 4 vs entry 3). The combination of Rh(acac)(CO)<sub>2</sub> and *rac*-BINAP gave **3aa** with an improved yield (21%), and less decarbonylation product **4aa** was formed (entry 5). Finally, the use of PhanePhos led to the best results in the series of the tested bidentate ligands. Thus, with Rh(acac)(CO)<sub>2</sub> and PhanePhos (10 mol % each), **3aa** was obtained in 48% yield, and no decarbonylation was observed (entry 6). Increasing the catalyst amount to 20 mol % gave **3aa** in 62% yield (entry 7). Among the monodentate phosphines, PPh<sub>3</sub> gave complexes with good catalytic activity. For example, in the presence of Rh(acac)(CO)<sub>2</sub> and PPh<sub>3</sub> (20 mol % each) hydroacylation product **3aa** was furnished in 66% yield (entry 8). Pleasingly we found that the catalyst loading

could be decreased upon addition of MeCN. Presumably, the nitrile group coordinated to the rhodium center, thereby stabilizing relevant catalytic intermediates.<sup>11</sup> In this manner, the yield of **3aa** remained almost the same when only 10 mol % (each) of Rh(acac)(CO)<sub>2</sub> and PPh<sub>3</sub> were applied (entry 9).

Commonly, an electron-rich ligand coordinated to a metal center in low oxidation state can be expected to positively affect a hydroacylation reaction because it facilitates the C–H bond activation step.<sup>12</sup> However, the electronic properties of the ligand will also influence the later stages of the catalysis. Assuming that complexes of the type [(RCO)RhH(olefin)L<sub>n</sub>]<sup>+</sup> are formed, a positive effect could result from the presence of an electron-deficient ligand. This is particularly true for reactions with electron-rich substrates, where the olefin insertion barrier is reduced.<sup>13</sup> On the basis of that hypothesis, fluoro-substituted P(*p*-F-Ph)<sub>3</sub> was employed, and to our delight we found that with Rh(acac)(CO)<sub>2</sub> and this electron-deficient ligand the reactions furnished **3aa** in much better yields than before (up to 90%). Furthermore, the addition of MeCN was not necessary anymore (Table 1, entries 10 and 11).

Next, various salicylaldehydes **1** were subjected to the hydroacylation with 1-vinyl-2-pyrrolidinone (**2a**) in the presence of Rh(acac)(CO)<sub>2</sub> and PPh<sub>3</sub> or P(*p*-F-Ph)<sub>3</sub> (Table 2, conditions A and B, respectively). Electron-donating substituents (methyl, *tert*-butyl, and methoxy) in the 3 or 5 position had no significant effect on the hydroacylation reaction, and reactions with salicylaldehydes **1b–e** furnished addition products **3ba–ea** in good yields and high selectivity (entries 1–4). Salicylaldehydes **1f** and **1g** with 5-chloro and 5-fluoro substituents, respectively, also reacted with **2a**, but the yields of the corresponding products, **3fa** and **3ga**, were lower (entries 5 and 6). This finding was attributed to their more difficult C–H activation in the initial phase of the catalysis. The hydroacylation of **2a** with 2-hydroxy-1-naphthaldehyde (**1h**) gave **3ha** in high yield (entry 7).

Note that in all cases only the branched addition products were formed. The lack of linear products may be a result of the electronic properties of the enamide moiety which affected the carbon–carbon double bond polarity.<sup>14</sup>

Unfortunately, under the same conditions, enamide **2a** did not react with benzaldehyde. Apparently, the phenolic hydroxyl of the salicylaldehydes served as directing group being crucial for the success of the transformations.

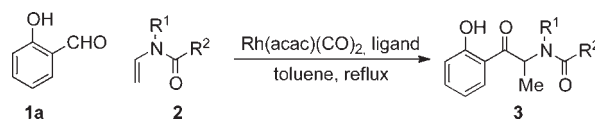
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**Table 3.** Hydroacylations of Enamides **2b–e** with Salicylaldehyde (**1a**)<sup>a</sup>



entry	<b>2</b>	[Rh] (mol %)	ligand (mol %)	product	yield (%)
1		20	Phanephos (20)		66
2		10	Phanephos (15)		69 <sup>b</sup>
3		20	PPh <sub>3</sub> (20)		70
4		10	PPh <sub>3</sub> (15)		75 <sup>b</sup>
5		10	PPh <sub>3</sub> (15)		47 <sup>b</sup>
6		20	PPh <sub>3</sub> (20)		54 (B:L=8:1)
7		10	PPh <sub>3</sub> (15)		99 (B:L=1:2) <sup>b</sup>

<sup>a</sup> Rh(acac)(CO)<sub>2</sub> (10 or 20 mol %) and ligand (15 or 20 mol %) were stirred in toluene (0.3 mL) for 1 h at room temperature, and then **1a** (0.3 mmol) and **2** (1.8 mmol) were added. The reaction mixture was heated to reflux for 48 h. <sup>b</sup> MeCN (6 equiv) was added.

Analogous observations have also been made in hydroacylations of other substrates, where the presence of coordinating groups proved essential as well.<sup>1–4,6,7</sup>

To further examine the scope of the reaction, enamides **2b–e** were reacted with salicylaldehyde (**1a**). To our surprise, the use of the rhodium complex derived from Rh(acac)(CO)<sub>2</sub> and P(*p*-F-Ph)<sub>3</sub> as ligand did not lead to satisfying results, and thus, for those reactions Phanephos and PPh<sub>3</sub> were selected as representative ligands. The results are summarized in Table 3. Hydroacylations of acyclic *N*-methyl-*N*-vinylacetamide (**2b**) with **1a** in the presence of the Rh(acac)(CO)<sub>2</sub>/Phanephos catalyst furnished **3ab** in yields up to 69% (entries 1 and 2). Also in this case, the addition of MeCN allowed reduction of the rhodium loading from 20 to 10 mol %. Using PPh<sub>3</sub> instead of Phanephos as ligand lowered the yield (data not shown in Table 3). *N*-Vinylacetamide (**2c**) having a hydrogen atom at the amide nitrogen also reacted with **1a** to afford **3ac** in up to 75% yield (entries 3 and 4). The reaction of *N*-vinylcaprolactam **2d** with **1a** gave **3ad** in 47% yield. In both cases, the best results were obtained by addition of MeCN (6 equiv) to a catalyst prepared from 10 mol % of Rh(acac)(CO)<sub>2</sub> and 15 mol % of PPh<sub>3</sub> (Table 3, entries 4 and 5). Finally, starting from *N*-vinylphthalimide (**2e**) and **1a** the formation of two regioisomeric products, **3ae** and **3ae'**, was observed. In the absence of MeCN, they were isolated in

54% overall yield with branched **3ae** as the major product (entry 6). However, when the standard conditions (with 10 mol % of Rh(acac)(CO)<sub>2</sub>, 15 mol % of PPh<sub>3</sub> and 6 equiv MeCN) were used the yield increased to 99%, but now, linear **3ae'** became the major isomer. Presumably, the nitrile coordinates to the metal altering the catalyst structure.

In summary, a rhodium-catalyzed regioselective intermolecular hydroacylation of enamides with salicylaldehydes has been developed. It represents an atom-economic method for the synthesis of  $\alpha$ -amido ketones. Studies with the goal to further extend the substrate scope and to develop asymmetric variants of this transformation are in progress.

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**Supporting Information Available.** Experimental procedures and analytical data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.