# Rh-Catalyzed Asymmetric Hydroaminomethylation of $\alpha$ -Substituted Acrylamides: Application in the Synthesis of RWAY

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**ABSTRACT:** The successful rhodium-catalyzed asymmetric hydroformylation and hydroaminomethylation of  $\alpha$ -substituted acrylamides is described using 1,3-phosphite-phosphoramidite ligands based on a sugar backbone. A broad scope of chiral aldehydes and amines were afforded in high yields and excellent enantioselectivities (up to 99%). Furthermore, the synthetic potential of this method is demonstrated by the single-step synthesis of the brain imaging molecule RWAY.

T he Rh-catalyzed hydroaminomethylation (HAM) of alkenes into amines is a sustainable, atom-economic, single-step alternative to classical multistep synthetic routes.<sup>1</sup> Although the enantioselective version of this reaction has a high potential, there are only a few examples reported to date and all of them require either sacrificial reagents or cocatalysts to access the chiral amines (Scheme 1A). In consequence, the efficiency and interest regarding the reaction are undermined.<sup>2</sup> Recently, we reported the efficient Rh-catalyzed asymmetric HAM of  $\alpha$ -alkyl acrylates to access chiral  $\gamma$ -aminobutyric esters using a single Rh-catalyst (Rh/(R,R-QuinoxP\*) (Scheme 1B).<sup>3</sup> This work provided a straightforward access to chiral  $\gamma$ -aminobutyric acid (GABA) derivatives.<sup>4,5</sup>

Among the GABA derivatives, those that contain an amide group are of paramount importance because this motif is present in CCR2 antagonists for chronic inflammatory processes such as atherosclerosis, multiple sclerosis, and rheumatoid arthritis<sup>6</sup> and CCR5 antagonists for HIV drug,<sup>7a</sup> or for brain imaging.<sup>7b</sup>

In this work we present a new, direct atom-efficient route to obtain amide-based GABA derivatives based on the Rhcatalyzed asymmetric HAM of  $\alpha$ -substituted acrylamides (Scheme 1C). Since enantioselectivity in this process is induced during the hydroformylation (HF) step, the discovery of an efficient chiral catalyst is fundamental to economically achieve those amide-based GABA derivatives. The complexity of this problem can be understood by noticing that  $\alpha$ substituted acrylamides are a particular case of 1,1'- disubstituted olefins. The hydroformylation of 1,1'-disubstituted olefins has been less studied than other mono- and disubstituted olefins, with only a few successful reported examples<sup>8,10</sup> and earlier ligands that were efficient for mono- and 1,2-disubstituted olefins (e.g., Binaphos, diazaphospholane, and Kelliphite), did not work well for 1,1'-disubstituted olefins.<sup>10a</sup> In addition, small structural changes from one type of 1,1'-disubstituted olefin to another may require significant changes in ligand structure and reaction conditions. Therefore, an approach based on fine-tuning modular ligands can be advantageous to advance in the hydroformylation of 1,1'-disubstituted olefins, and therefore in the HF of  $\alpha$ -substituted acrylamides.

To the best of our knowledge, the asymmetric hydroformylation of  $\alpha$ -substituted acrylamides has been reported only for two substrates, with ee's up to 86%, using a Rh/ DTBN-YanPhos system.<sup>8,9</sup> Apart from this very recent work, no other catalytic systems have been reported that can hydroformylate a large series of  $\alpha$ -substituted acrylamides.

We first searched for appropriate ligands for the hydroformylation of  $\alpha$ -substituted acrylamides. The results are

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# Scheme 1. Selected Precedents in Rh-Catalyzed Asymmetric HAM of Alkenes

A) Previous work on Rh-catalyzed asymmetric hydroaminomethylation



B) Rh-cat. asymmetric HAM of  $\alpha$ -alkyl acrylates (our group, 2019)



C) This work: Rh-cat. asymmetric HF and HAM of α-substituted acrylamides



described in Table 1. We tested ligands that were previously presented as efficient in the hydroformylation of 1,1disubstituted olefins  $(L1-L3)^{10a}$  and mono- and 1,2disubstituted olefins  $(L4-L5)^{.10a}$  Inspired by the phosphinephosphoroamidite YanPhos-based ligands that were successfully used in the hydroformylation of some 1,1'-disubstituted olefins, we also considered the new phosphite-phosphoramidite ligand L6 that contains a sugar backbone and is air stable. <sup>11</sup> Ligands L1–L6 were tested using the commercially available substrate *N,N*-diethylmethacrylamide 1a, [Rh(aca)-(CO)<sub>2</sub>] as the Rh precursor, and toluene as the solvent, under 10 bar of H<sub>2</sub>/CO (1:1), at 90 °C for 16 h (Table 1).

Under these conditions, the catalysts bearing the diphosphines (R,R)-QuinoxP\* L1 (entry 1), (R,R)-BenzP\* L2 (entry 2), and (S,S)-Ph-BPE L3 (entry 3) were barely active (conversions <5%). It is noteworthy that L2 had provided high yields (up to 91%) and high enantioselectivities (up to 94%) in the hydroformylation of  $\alpha$ -alkyl acrylates.<sup>10c,d</sup> This stresses the comments in the introduction that small structural changes in the 1,1'-disubstituted olefin may require significant changes in ligand structure. Electronic and/or steric differences between the esters and the amides thus make the hydroformylation of the latter more difficult. Using the phosphinephosphite  $(S_{av}S,S)$ -Bobphos L4 (entry 4) and the sugar based diphosphite L5 (entry 5), the conversion increased to 64% and 74% respectively, with good regio- and chemoselectivity of the linear product 2a. However, enantioselectivities were poor (ca. 8%) in both cases. Interestingly, full conversion, high regioand chemoselectivity of the desired linear aldehyde 2a, and 

 Table 1. Screening of Ligands for the Asymmetric

 Hydroformylation of N,N-Diethylmethacrylamide 1a



Liftiy	Ligand	/0 COIIV	70 2a [11]	1/0 1410	10 00
1	L1	8	38	5	-
2	L2	0	-	-	-
3	L3	0	-	-	-
4	L4	64	76 [44]	25	4
5	L5	74	83 [53]	28	8
6	L6	99	90 [86]	100/0	73

<sup>*a*</sup>Reaction conditions: 1a (0.5 mmol), Rh =  $[Rh(acac)(CO)_2]$  (1 mol %), L (1.2 mol %), P = 10 bar (H<sub>2</sub>/CO, 1:1), toluene (0.4 mL), T = 90 °C, t = 16 h, 900 r.p.m. <sup>*b*</sup>% Conversions and yields determined by <sup>1</sup>H NMR spectroscopy using naphthalene as internal standard; values in brackets refer to isolated yields. <sup>*c*</sup>% ee of 2a determined by chiral GC after reduction into the alcohol.

high enantioselectivity (73%) were obtained with the sugar based phosphite-phosphoramidite L6 (entry 6).

We next studied the effect of temperature, total pressure, and CO/H<sub>2</sub> ratio on the selectivity in the hydroformylation of *N*,*N*-diethylmethacrylamide **1a** (see Table S1 for details). Under optimized reaction conditions (T = 60 °C, 20 bar, H<sub>2</sub>/ CO = 1:1), the enantioselectivity increased up to 90%, maintaining high regio- and chemoselectivity for the desired linear aldehyde **2a** (Table 2, entries 1 and 2).

We next studied the effects of several ligand parameters.<sup>12</sup> Since previous reports on the hydroformylation of 1,1'disubstituted substrates showed that small variations in the ligands can significantly affect the catalytic performance, we first modified the substituent at the nitrogen atom (Table 2). The enantioselectivity decreased with the less sterically hindered ligands L7 and L8 (entries 3 and 4). Ligands containing an (S)- isopropyl group L9 and a methyl benzyl group L10 also decreased the catalytic performance, but high yields (up to 76%) and high enantioselectivities (up to 85%) could still be obtained (entries 5 and 6). Finally, with ligand L11, that contained a tert-butyl group, 92% enantioselectivity was achieved but at the cost of conversion (49%, entry 7), which suggests that alkene coordination is more difficult when steric hindrance is increased. In conclusion, the ligand L6 provided the best compromise between activity and enantioselectivity. Finally, the effect of the binaphthol's configurations was studied (see Table S2 for details). The best results were obtained with S configurations in both biaryl moieties while  $(S_N, R_O)$ ,  $(R_N, S_O)$ , and  $(R_N, R_O)$  configurations provided very low conversion as well as low regio- and chemoselectivity for the linear aldehyde 2a.

Table 2. Influence of Ligand Variations on the Asymmetric Hydroformylation of 1a



<sup>*a*</sup>Reaction conditions: **1a** (0.5 mmol), Rh = [Rh(acac)(CO)<sub>2</sub>] (1 mol %), L (1.2 mol %), P = 20 bar (H<sub>2</sub>/CO, 1:1), toluene (0.4 mL), T = 60 °C, t = 16 h, 900 r.p.m. <sup>*b*</sup>% Conversions and yields determined by <sup>1</sup>H NMR spectroscopy using naphthalene as internal standard; values in brackets refer to isolated yields. In all cases, the % of branched products was <5%. <sup>*c*</sup>% ee of **2a** determined by chiral GC after reduction into the alcohol. <sup>*d*</sup>t = 48 h.

At this stage, the asymmetric hydroformylation of a set of  $\alpha$ substituted acrylamides was tested using ligand L6 (Scheme 2). Three substrates with distinct amide substituents were first



<sup>*a*</sup>As Table 2 (entry 2), Isolated yields, average of two independent runs. <sup>*b*</sup>% ee determined by chiral GC or HPLC after reduction into the alcohol. <sup>*c*</sup>I (0.25 mmol), Rh (2 mol %). <sup>*d*</sup>T = 90 °C, t = 16 h. <sup>*e*</sup>Isolated yield corresponds to alcohol after reduction of the crude.

compared. For the substrate 1b, bearing a diphenyl amide moiety, a 50% yield of 2b with 80% ee was obtained. Better results, 80% yield and an excellent 99% ee, were obtained for the formation of the linear aldehyde 2c that contains a diisopropyl amide substituent. Next, the effect of the substituent in the  $\alpha$ -position was investigated. Products 2d and 2e bearing ethyl and benzyl groups were obtained in high yields (up to 74%), together with 90% and 86% ee, respectively (Scheme 2). A lower yield and poor enantioselectivity were obtained with a more sterically hindered alkene (linear aldehyde 2f). For this substrate, we conducted a brief screening with ligands L6-L11 (see Tables S3 and S4 in SI), and using ligand L10 instead of L6, the linear product 2f could be obtained in 66% yield and 74% ee. As in the case of 2f, L10 also provided high yields and enantioselectivities (up to 82%) for the linear aldehyde 2g bearing a cyclopentyl group and the linear aldehyde 2h containing a phenyl group. Finally, 2i bearing a phenyl group in the  $\alpha$ -position and an azepanamide group was also obtained in good yield (52%) and high enantioselectivity (74%). The results for 2h and 2i are particularly relevant since important biologically active molecules include a phenyl substituent in  $\alpha$ -position (Scheme 2) and the catalysts reported to date  $^{3,8,10c}$  were only efficient for  $\alpha$ -alkyl substituted substrates. The catalytic systems based on phosphite-phosphoramidite ligands L6 and L10 are thus efficient in the Rh-catalyzed asymmetric hydroformylation of  $\alpha$ -substituted acrylamides (ee up to 99%), even for substrates with a phenyl group in  $\alpha$ -position. It is noteworthy that, in all cases, only a small amount of branched product was formed (<5%).

Based on these results, our Rh/phosphite-phosphoroamidite catalysts were tested in the one-pot asymmetric HAM of  $\alpha$ substituted acrylamides to directly yield chiral amines.<sup>1</sup> A brief optimization of the reaction conditions was first conducted with alkene 1a and morpholine 3a as the nucleophile (see Table S5 in SI). With ligand L6 and  $[Rh(acac)(CO)_2]$  in a mixture of 1,2-dichloroethane (DCE)/toluene as solvent under 20 bar of  $H_2/CO$  (2:1) at 90 °C, the GABA derivative 4a was obtained in 79% yield and 85% ee (Scheme 3).<sup>13</sup> Note that this experiment was performed at 1 mmol scale without affecting the yield or the enantioselectivity (see Section SXVI in the SI). Next, a series of other secondary amines were also tested in the asymmetric HAM of 1a (Scheme 3), and the products 4b-d were obtained in good-to-high yields (up to 75%) and high enantioselectivities (up to 85%). Interestingly, protecting groups such as benzyl and Boc (4b and 4c) were perfectly tolerated. Even for primary amines such as aniline, the product 4e was afforded in 56% yield and 78% ee. When other acrylamides were used (Scheme 3 bottom), the GABA derivatives 4 were invariably obtained in good-to-high yields (up to 78%) and high enantioselectivities (up to 84%), and the trends observed in hydroformylation were again observed in the HAM reaction (Scheme 3). Thus, a slight decrease in enantioselectivity was observed for the product 4g that contains two phenyl groups in the amide, while dialkyl substituted acrylamides (4f,h,i) provided the best results.

Substrates 4d and 4k are of particular interest (Scheme 3) since they contain either the amine (4d) or the amide (4k) that are present in the brain imaging molecule RWAY (Scheme 1), and for both cases the product was obtained in high enantioselectivities (up to 84%). In view of these results, we envisioned the synthesis of RWAY in a single step via the Rh-catalyzed asymmetric hydroaminomethylation (Scheme 4).

# Scheme 3. Rh-Catalyzed Asymmetric HAM of Acrylamides $^{a,b}$





<sup>*a*</sup>**1** (0.5 mmol), **3** (0,5 mmol), Rh =  $[Rh(acac)(CO)_2]$  (1 mol %), **L6** (1.2 mol %), *P* = 20 bar (H<sub>2</sub>/CO, 2:1), *T* = 90 °C, *t* = 16 h. Isolated yields, average of two independent runs. <sup>*b*</sup>% ee determined by chiral HPLC. <sup>*c*</sup>**1** (0.25 mmol), **2** (0.25 mmol), Rh (2 mol %), **L6** (2.4 mol %).





<sup>*a*</sup>**Ib** (0.25 mmol), **3b** (0.25 mmol), Rh =  $[Rh(acac)(CO)_2]$  (2 mol %), **L6** (2.4 mol %), *P* = 20 bar (H<sub>2</sub>/CO, 2:1), *T* = 90 °C, *t* = 16 h. Isolated yields, average of two independent runs. <sup>*b*</sup>% ee determined by chiral HPLC.

Under previous optimized conditions (Scheme 3), a precipitate was generated and the conversion dropped significantly. However, when a mixture of 2-methyl-tetrahydrofuran (2-Me-THF) and toluene was used, the RWAY compound **4I** was obtained in 64% isolated yield and 82% ee (Scheme 4).<sup>14</sup>

In summary, we have developed an efficient system for the Rh-catalyzed asymmetric HF and HAM of  $\alpha$ -substituted acrylamides using chiral phosphite-phosphoramide ligands. In both reactions, the products 2 and 4 were obtained in good to

high yields with high to excellent enantioselectivities. The system could tolerate different substituents at the acrylamide for both reactions, and in the case of HAM, various secondary amines and aniline could be applied. Furthermore, the synthesis of RWAY was performed in one step, with good yield and high enantioselectivity. These results open up the use of new air stable, readily available, and modular ligands to advance in the hydroformylation of 1,1'-disubstituted olefins. Mechanistic studies are currently ongoing.

# ASSOCIATED CONTENT

#### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03433.

Experimental details for the preparation and characterization of ligands L6-L11 and of acrylamide substrates 1, and for the catalytic testing (optimization and analytical methods) are included. (PDF)

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#### Notes

The authors declare no competing financial interest.

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(11) The synthesis of ligand L6 is described in the Supporting Information.

(12) The synthesis of ligands L7–L11 is described in the Supporting Information.

(13) Depending on the substrates, it was necessary to slightly modify the reaction conditions. See Supporting Information for detailed information on the reaction contiditions.

(14) See Supporting Information for detailed information on the optimization of the reaction conditions.