Rh-catalyzed asymmetric hydroaminomethylation of α-substituted acrylamides: application in the synthesis of RWAY.

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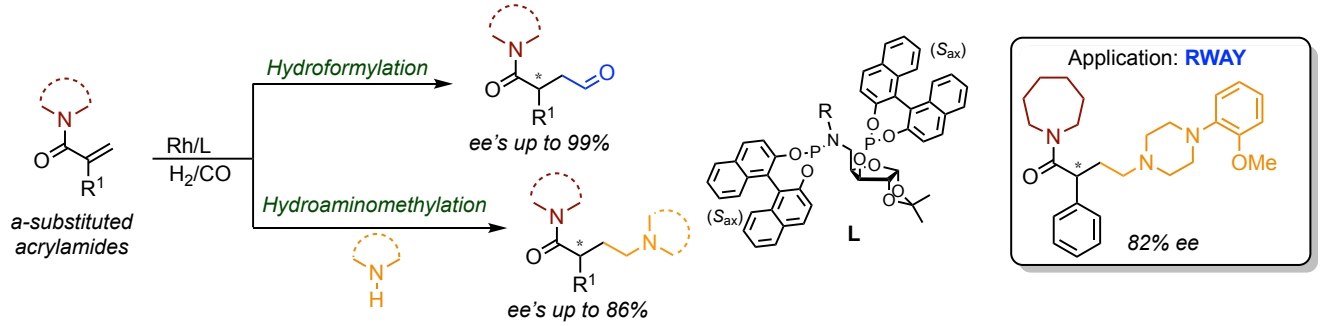
Supporting Information Placeholder



ABSTRACT: The successful rhodium-catalyzed asymmetric hydroformylation and hydroaminomethylation of α-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.

The Rh-catalyzed hydroaminomethylation (HAM) of alkenes into amines is a sustainable, atom-economic, single step alternative to classical multistep synthetic routes.[1] 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 co-catalysts to access the chiral amines (Scheme 1A). In consequence, the efficiency and interest of the reaction is undermined.[2] Recently, we reported the efficient Rh-catalyzed asymmetric HAM of α-alkyl acrylates to access chiral γ-aminobutyric esters using a single Rh-catalyst (Rh/(*R*,*R*-QuinoxP*) (Scheme 1B).[3] This work provided an straightforward access to chiral γ-aminobutyric acid (GABA) derivatives.[4,5]

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,[6] and CCR5 antagonists for HIV drug,[7a] or for brain imaging.[7b]

In this work we present a new, direct atom-efficient route to obtain amide-based GABA derivatives based on the Rh-catalyzed asymmetric HAM of α-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 α-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[8,10] 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.[10a]. 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 α-substituted acrylamides.

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

Scheme 1. Selected precedents in Rh-cat. asymmetric HAM of alkenes

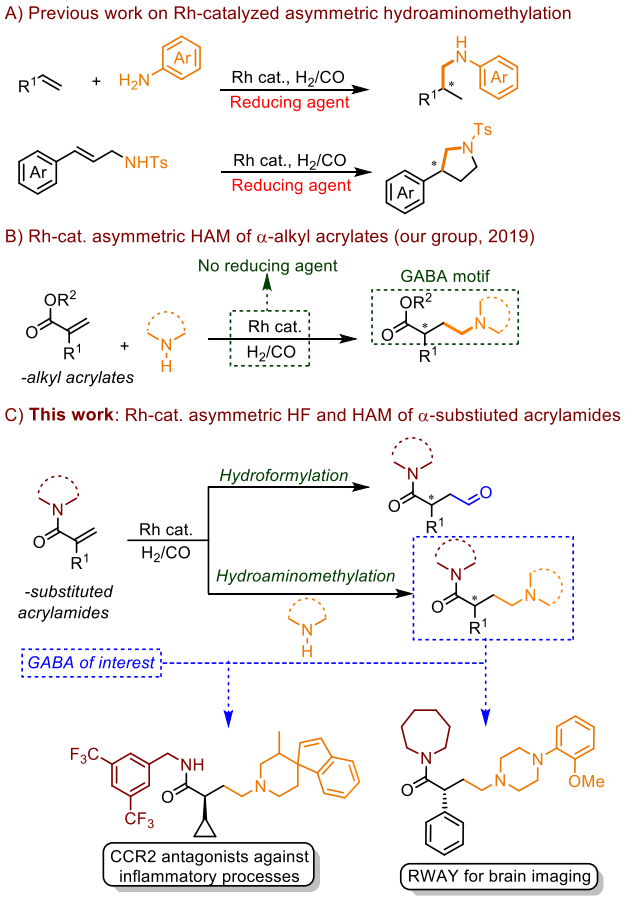
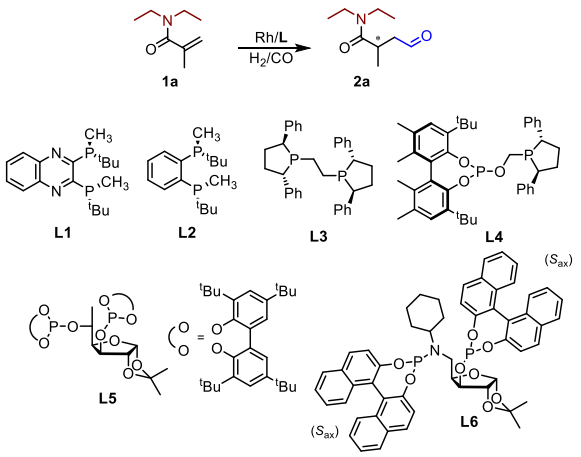


Table 1. Screening of ligands for the asymmetric hydroformylation of N,N-diethylmethacrylamide 1a



Entry[a]	Ligand	% Conv.[b]	% **2a** [IY][b]	l/b ratio	% *ee*[c]
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

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

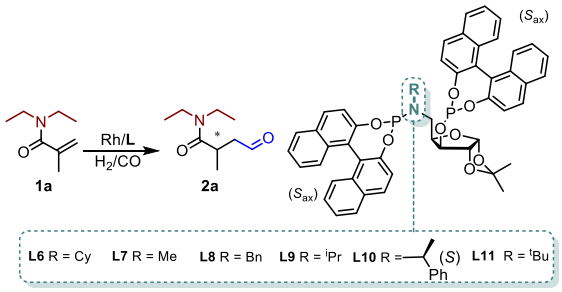
We first searched for appropriate ligands for the hydroformylation of α-substituted acrylamides. The results are described in Table 1. We tested ligands that were previously presented as efficient in the hydroformylation of 1,1-disubstituted olefins (**L1**-**L3**)[10a] and mono and 1,2- disubstituted olefins (**L4**–**L5**).[10a] Inspired by the phosphine-phosphoroamidite 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.[11] Ligands **L1**-**L6** were tested using the commercially available substrate N,N-diethylmethacrylamide **1a**, [Rh(acac)(CO)$_2$] as Rh precursor, toluene as solvent, under 10 bar H$_2$/CO (1:1), at 90 °C during 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 α-alkyl acrylates.[10c,d] 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 phosphine-phosphite (S_{ax},*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 regio- and chemoselectivity of the desired linear aldehyde **2a** and 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$_2$ 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$_2$/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[12]. 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, low regio- and low chemoselectivity for the linear aldehyde **2a**.

Table 2. Influence of ligand variations on the asymmetric hydroformylation of 1a

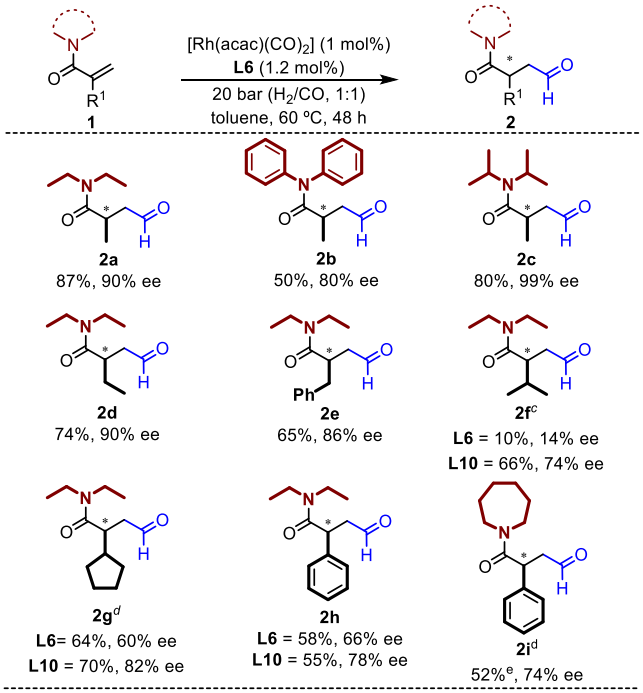


Entry[a]	Ligand	% Conv.[b]	% **2a** [IY][b]	% ee[c]
1	L6	72	89 [64]	90
2	L6	99	88 [87]	90[d]
3	L7	54	84 [45]	74
4	L8	76	82 [60]	70
5	L9	70	86 [60]	81
6	L10	68	82 [53]	85
7	L11	49	84 [38]	92

[a] Reaction conditions: **1a** (0.5 mmol), Rh = [Rh(acac)(CO)$_2$] (1 mol%), **L** (1.2 mol %), P = 20 bar (H$_2$/CO, 1:1), toluene (0.4 mL), T = 60 °C, t = 16 h, 900 r.p.m. [b] % Conversions and yields determined by ^{1}H NMR spectroscopy using naphthalene as internal standard, values in brackets refer to isolated yields. In all cases, the % of branched products was <5%. [c] % ee of **2a** determined by chiral GC after reduction into the alcohol. [d] t= 48 h.

At this stage, the asymmetric hydroformylation of a set of α-substituted acrylamides was tested using ligand **L6** (Scheme 2). Three substrates with distinct amide substituents were first compared. For the substrate **1b,** bearing a diphenyl amide moiety, 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 α-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 Table S3 and S4 in ESI), and using ligand **L10** instead of **L6,** the linear product **2f** could be obtained in 66% yield and 74% ee. Like for **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 α-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 α-position (Scheme 2) and the catalysts reported to date[3,8,10c] were only efficient for α-alkyl substituted substrates. The catalytic systems based on phosphite-phosphoramidite ligands **L6** and **L10** are thus efficient in the Rh-catalyzed asymmetric hydroformylation of α-substituted acrylamides (ee up to 99%), even for substrates with a phenyl group in α-position. It is noteworthy that in all cases, only a small amount of branched product was formed (<5%).

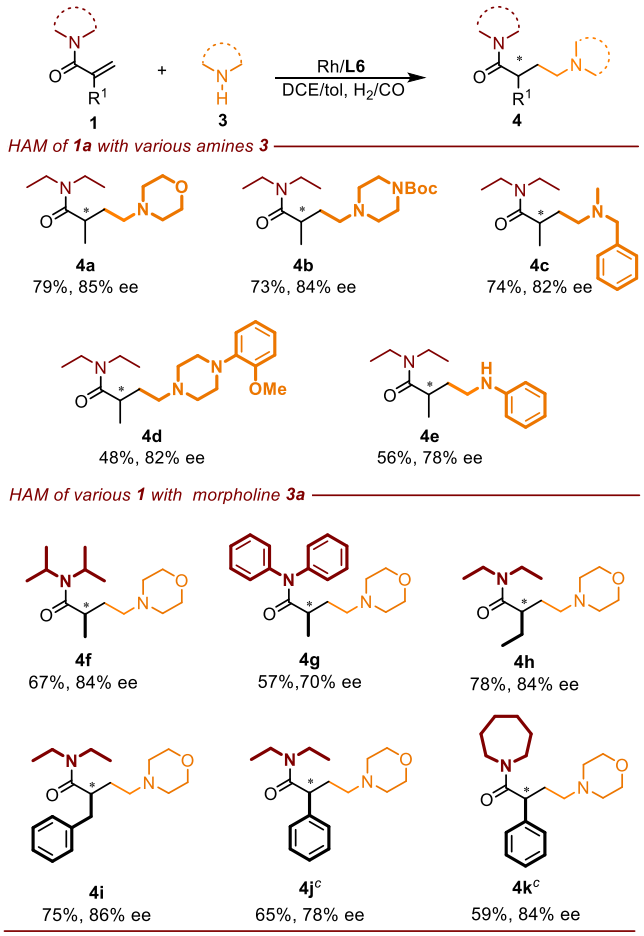
Scheme 2. Asymmetric hydroformylation of acrylamides[a,b]



[a] As Table 2 (entry 2). Isolated yields, average of two independent runs. [b] % ee determined by chiral GC or HPLC after reduction into the alcohol. [c] **1** (0.25 mmol) Rh (2 mol%). [d] T = 90 ºC, t = 16h. [e] Isolated yield corresponds to alcohol after reduction of the crude.

Based on these results, our Rh/phosphite-phosphoroamidite catalysts were tested in the one pot asymmetric HAM of α-substituted acrylamides to directly yield chiral amines.[1] A brief optimization of the reaction conditions was first conducted with alkene **1a** and morpholine **3a** as nucleophile (See Table S5 in ESI). 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).[13] Note that this experiment was performed at 1 mmol scale without affecting the yield nor the enantioselectivity (See Section SXVI in 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.

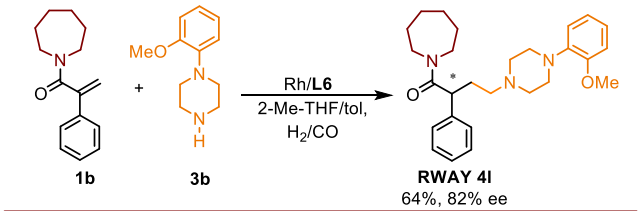
Scheme 3 Rh-cat. asymmetric HAM of acrylamides[a,b]



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

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

Scheme 4. Synthesis of RWAY 4l via HAM reaction[a,b]



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

In summary, we have developed an efficient system for the Rh-catalyzed asymmetric HF and HAM of α-substituted acrylamides using chiral phosphite-phosphoramide ligands. In both reactions, the products **2** and **4** were obtained good to high yields and 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 on the ACS Publications website.
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.

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Notes

The authors declare no competing financial interests.

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

(12) The synthesis of ligands **L7-L11** is described in Supporting Information.

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

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