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# Ligand-Controlled Regiodivergent Hydroformylation of Ynamides: A Stereospecific and Regioselective Access to 2- and 3-Aminoacroleins

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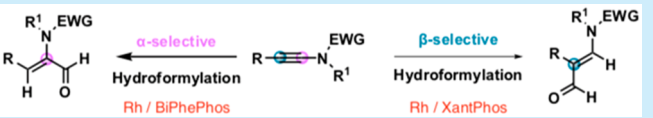
Supporting Information

**ABSTRACT:** The rhodium-catalyzed hydroformylation of ynamides is described and gives selective access to 2- or 3-aminoacrolein derivatives. The regioselectivity of this carbonylation can be completely controlled at will thanks to the nature of the ligand used. This represents the first example of regiodivergent alkyne hydroformylation. The influence of the substituents on the different positions of the ynamide has been investigated, and it appears that this reaction is tolerant to a wide range of functional groups.






Eighty years after having been discovered by Roelen,[1] hydroformylation reaction has demonstrated over the decades its strong synthetic power and became the most important homogeneous catalytic process in the industry.[2,3] This reaction is highly atom economic, as it functionalizes a carbon−carbon multiple bond with an aldehyde generated from readily available gases (i.e., CO and $H_2$), and its relatively mild reaction conditions have allowed it to be used as the key transformation in elegant tandem/domino processes.[4] Since its first report by Wender in 1957,[5] alkyne hydroformylation has been much less investigated than that of alkenes.[6] In recent years, major progress has been made in alkyne hydroformylation. One of the most notable is Buchwald's introduction of BiPhePhos as ligand in rhodium-catalyzed hydrocarbonylation,[7] allowing a significant decrease in the overreduction of the newly formed $\alpha,\beta$-unsaturated aldehyde. Since then, significant efforts have been done by several groups such as Alper,[8] Hidai,[9] le Floch and Sanchez,[10] Breit,[11] Beller,[12] and Dong and Zhang[13] in order to increase the regio-/stereoselectivity and to suppress as much as possible the byproducts coming from undesired hydrogenation processes. In addition, very recently, You[14] introduced the first syngas-free alkyne hydroformylation. However, if the overreduction can be now considered as controlled, in the case of internal dissymmetric alkynes a lot of work remains to be done in terms of regiocontrol of the reaction. To date, three possibilities of control have been investigated (Figure 1). The first relies on the classical steric control. In that case the metal center will be introduced on the less hindered side of the alkyne. The second is based on the use of phenylacetylene derivatives. In that specific case, the reaction mainly drives to the introduction of the formyl group on the same carbon as the aromatic moiety.

The third option is the use of a directing group that can chelate the metal center of the catalytic species. And finally, the last one has been recently reported by Breit and co-workers.[15] They demonstrated that a rhodium-catalyzed tandem regioselective hydroformylation/hydrogenation of internal alkynes can be performed thanks to the use of a guanidine-based ligand that allows supramolecular interactions between the organometallic complex and the substrate. If all these approaches can lead from good to very good regioselectivity;

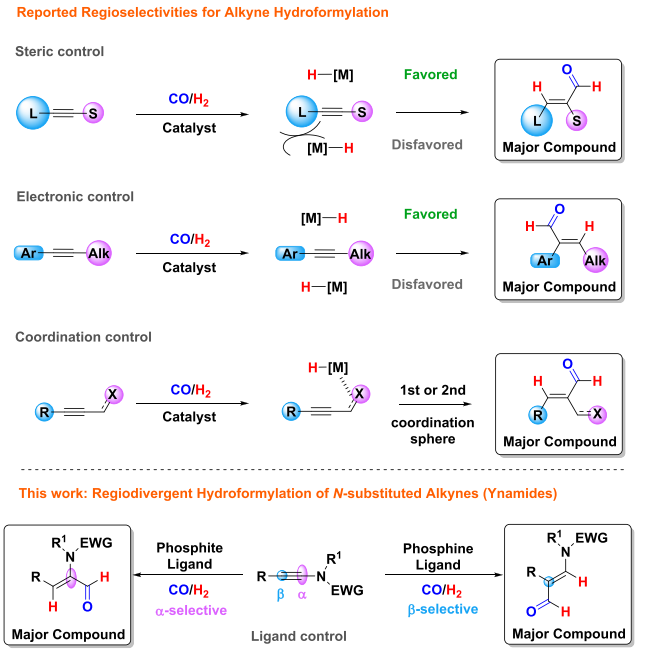



**Figure 1.** Comparison between reported alkyne−hydroformylation regioselectivity and this work reporting the ligand-controlled regiodivergent hydroformylation of ynamides.

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notably, in all cases, its controlled inversion has never been reported.

In this context, we have decided to focus our attention on the use of particular alkynes directly linked to a nitrogen atom, namely the ynamides.[16] These compounds have emerged over the last 15 years as remarkable building blocks. Notably, they are precious precursors of polysubstituted enamines that can be subsequently involved in the synthesis of valuable complex molecules. In our opinion, this family of molecules could be quite interesting as hydroformylation substrates for several reasons. First, the use of these species in hydroformylation could lead to efficient and general access to polyfunctionalized aminoacrolein derivatives that are building blocks with high synthetic potential but fairly difficult to synthesize.[17] Second, ynamides are particular unsymmetrical alkynes. On the one hand, due to the presence of the nitrogen atom linked to the carbon−carbon triple bond, this unsaturation is remarkably electron rich. This activation could result in a high tendency to be directly hydrogenated to form the corresponding enamine **4**, but its strong polarization could also help to control the regioselectivity of the hydroformylation reaction. On the other hand, the electron-withdrawing group attached to the nitrogen can act as a directing group and could also favor one regioisomer over the other.[18] All together, these parameters represent as many challenges but, being tamed, they can be regarded as an asset to regioselectively perform the hydroformylation to obtain at will an isomer or the other (**2** or **3**).[19] In this paper, we demonstrate that ynamides undergo efficient regiodivergent ligand-controlled hydroformylations with good to very good selectivity. To the best of our knowledge, this is the first example of a regiodivergent hydroformylation of alkynes (Figure 1).

To begin our investigations, a simple ynamide **1a** bearing an alkyl chain on both the nitrogen and the alkyne and a tosyl group as the electron-withdrawing group was chosen as the substrate, and the most efficient conditions reported in the literature for the hydroformylation of alkyne were first tested (i.e., triphenylphosphine as ligand, toluene as solvent at 70 °C under 5 bar of syngas overnight) (Table 2, entry 1). The reaction took place with a very low conversion. The main product formed was the reduced compound **4a** (68% of the converted material), but traces of the targeted aldehydes have been detected, and the NMR analyses showed that the $\beta$ isomer **3a** was clearly favored (ratio **2a**/**3a** = 25/75). To improve this first encouraging result, we have then decided to test different ligands to evaluate their effect on the overall reaction results. Remarkably, when the ligand was changed to $P(OPh)_3$ the conversion increased, but more interestingly, the ratio **2a**/**3a** was completely inverted (Table 2, entry 2). Taken together these two results were validating our idea that the regioselectivity of the hydroformylation of ynamides could be controlled in one direction or the other. After testing of several bidentate ligands (Xantphos,[20] (*R*)-DM-SEGPHOS,[21] BiPhePhos,[22] TriBiPhos,[23] for structures see Table 1), only Xantphos and BiPhePhos (BPP) confirmed this differential selectivity between phosphine and phosphite ligands while increasing the conversion to a synthetically useful level (Table 2, entries 3−6). However, if the reaction conditions seemed to be optimal when using Xantphos as ligand (high regioselectivity and only traces of direct hydrogenation), a significant amount of the reduced compound **4a** remained when BiPhePhos was used. Notably, the isomerization of the newly formed C−C double bond has never been observed as only the *Z* isomer was systematically obtained.

**Table 1. Optimization of the Reaction Conditions**

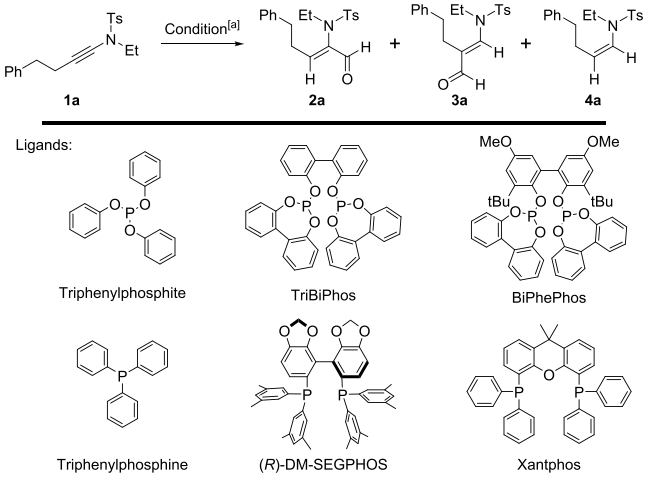


**Table 2. Ligand and Solvent Optimization**[a]

| entry | ligand | solvent | **2a**/**3a** | (**2a** + **3a**)/**4a** | yield ald (%)[c] |
|---|---|---|---|---|---|
| 1 | $P(Ph)_3$ | toluene | 25/75 | 32/68 | nd[b] |
| 2 | $P(OPh)_3$ | toluene | 71/29 | 54/46 | 38 |
| **3** | **Xantphos** | **toluene** | **5/95** | **92/8** | **75** |
| 4 | (*R*)-DM-SEGPHOS | toluene | nd | nd | nd[d] |
| **5** | **BiPhePhos** | **toluene** | **81/19** | **63/37** | **57** |
| 6 | TriBiPhos | toluene | nd | nd | nd[d] |
| 7 | BiPhePhos | hexane | 76/24 | 60/40 | 56 |
| 8 | BiPhePhos | DCE | 76/24 | 67/33 | 59 |
| 9 | BiPhePhos | $CH_3CN$ | 82/18 | 61/39 | 42 |

[a]$Rh(CO)_2(acac)$ (2 mol %), ligand (6 mol %), **1a** (1 equiv, 0.03 mol·$L^{-1}$), $CO/H_2$ (1:1, 5 bar), 70 °C, 16 h; ratios determined by $^1H$ NMR analysis of the crude. [b]Conversion = 15%. [c]Isolated yield of **2a** + **3a**. [d]Conversion <5%. nd = not determined.

To optimize the reaction conditions when BiPhePhos is used as ligand, we have investigated diverse additional parameters. First, to evaluate the effect of the solvent on the chelation of the directing group, we performed a quick screening (hexane, DCE, acetonitrile). Notably, the regioselectivity remained relatively unaffected by the nature of it (Table 2 entries 5−7). Then, pushing further our effort to reduce the fraction of the hydrogenated product **4a**, we have focused our attention on the gaseous part of the reaction. First, we demonstrated that the pressure of syngas ($CO/H_2$ 1:1) was not significantly influencing the efficiency and the selectivity of the reaction (Table 3 entries 1−3). Then we investigated the effect of the proportion of carbon monoxide. For practical reasons, we performed this study at 10 bar. Remarkably an enrichment in CO of the gas mixture resulted in a significant decrease of the quantity of **4a** formed without affecting the regioselectivity of the reaction (Table 3, entries 4 and 5). The aldehydes could be obtained in more than 75% yield. Notably, performing the reaction at 40 °C resulted in a very low conversion of the starting material after 16 h (less than 3%), while the reaction done at 100 °C gave the same results as at 70 °C. In addition, we determined that 16 h was required for complete conversion in both cases.



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**Table 3. Optimization of $CO/H_2$ Ratio and Pressure when BiPhePhos Used as Ligand[a]**

| entry | $CO/H_2$ | pressure (bar) | 2a/3a | (2a + 3a)/4a | yield ald (%)[b] |
|---|---|---|---|---|---|
| 1 | 1:1 | 5 | 81/19 | 63/37 | 57 |
| 2 | 1:1 | 10 | 75/25 | 70/30 | 60 |
| 3 | 1:1 | 2.5 | 79/21 | 65/35 | 55 |
| 4 | 3:1 | 10 | 71/29 | 82/18 | 77 |
| **5** | **5:1** | **10** | **70/30** | **84/16** | **75** |

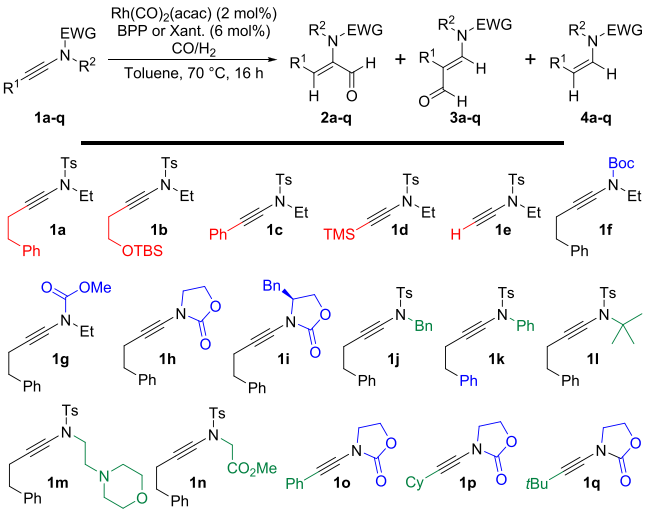
[a]$Rh(CO)_2(acac)$ (2 mol %), BiPhePhos (6 mol %), **1a** (1 equiv, 0.03 mol·$L^{-1}$), toluene, 70 °C, $CO/H_2$ (see table body), 16 h. Ratios determined by $^1H$ NMR analysis of the crude. [b]Isolated yield of **2a** + **3a**.

With these two optimized reaction conditions in hand (Xantphos and BiPhePhos), the scope of the reaction was investigated by performing both regiodivergent hydroformylations of diversely substituted ynamides (Table 4).

First, the influence of the substitution at the $\beta$ position of the ynamides has been evaluated. The functionalization of the alkyl chain with a protected alcohol for instance as in ynamide **1b** did not affect the selectivity of the reaction (entries 3 and 4) but induced a slight decrease of the yield around 10%. This could be potentially explained by the higher steric hindrance of the OTBS group in comparison to the previous phenyl ring. An aromatic ring such as a phenyl induced a remarkable increase of the direct reduction of **1c** to the corresponding enamine **4c** when BiPhePhos was used as ligand; however, the regioselectivity was improved with an 8/2 ratio in favor of **2c** (entry 5). Interestingly, apart from a slight increase of the proportion of reduced side product **4c**, the hydroformylation of **1c** using Xantphos as ligand gave similar results as **1a** in terms of yield and regioselectivity. A silylated substituent such as TMS on the ynamides **1d** led to complete inhibition of the reaction in both cases (entries 7 and 8) as only starting material was recovered after 16 h. To explain this phenomenon, if the steric hindrance can be incriminated when Xantphos is used as ligand, the additional electronic effect induced by the silicon atom on the polarization of the C−C triple bond has to be considered when BiPhePhos is employed (electronic impoverishment at the $\alpha$ position of the ynamide **1d**).

The use of terminal ynamide **1e** with BiPhePhos as ligand led to a significant increase in the reduced product **4e**. The low 26% yield observed and the apparent inversion of selectivity is most probably due to the degradation of the unstable enaminal **2e** (entry 9). In a second time, the influence of the protecting group on the nitrogen has been evaluated. In our opinion, this point was crucial as the selectivity of our catalytic systems is based on the directing abilities of this moiety. Substrates bearing a carbamate group such as Boc (**1f**), Moc (**1g**), or an oxazolidone (**1h** and **1i**) gave relatively similar results as the tosylated ynamide **1a** both in terms of selectivity and yield (entries 11−18). Then the effect of the last point of diversity, i.e., the second substituent on the nitrogen atom, was investigated. A benzyl group did not affect significantly the reactivity of the reaction as **1j** gave similar results as **1a** with both ligands (entries 19 and 20). An aniline-based ynamide **1k** gave better results with both ligands in term of selectivity, while the amount of the undesired reduction was significantly reduced (entries 21 and 22). A bulky substituent such as a *tert*-butyl group on the nitrogen of the ynamide **1l** led to complete inhibition of the reaction with both ligands (entries 23 and 24). Together with the observation made with the TMS group on the terminal position of **1d** , this seems to demonstrate that

**Table 4. Scope and Limitation of the Reaction[a]**




| entry | substrate | ligand | 2/3 | ald/red (2+3)/4 | yield ald[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | BiPhePhos | 70/30 | 84/16 | 75 |
| 2 | **1a** | Xantphos | 5/95 | 92/8 | 75 |
| 3 | **1b** | BiPhePhos | 68/32 | 86/14 | 67 |
| 4 | **1b** | Xantphos | 13/87 | 91/9 | 62 |
| 5 | **1c** | BiPhePhos | 80/20 | 62/38 | 54 |
| 6 | **1c** | Xantphos | 7/93 | 86/14 | 84 |
| 7 | **1d** | BiPhePhos | | | nr |
| 8 | **1d** | Xantphos | | | nr |
| 9 | **1e** | BiPhePhos | 22/78 | 45/55 | 26[c] |
| 10 | **1e** | Xantphos | 5/95 | 93/7 | 54[c] |
| 11 | **1f** | BiPhePhos | 78/22 | 89/11 | 66 |
| 12 | **1f** | Xantphos | 7/93 | >95/<5 | 68 |
| 13 | **1g** | BiPhePhos | 73/27 | 87/13 | 62 |
| 14 | **1g** | Xantphos | 11/89 | >95/<5 | 87 |
| 15 | **1h** | BiPhePhos | 70/30 | 85/15 | 68 |
| 16 | **1h** | Xantphos | 13/87 | >95/<5 | 75 |
| 17 | **1i** | BiPhePhos | 57/43 | 88/12 | 77 |
| 18 | **1i** | Xantphos | 5/95 | >95/<5 | 78 |
| 19 | **1j** | BiPhePhos | 60/40 | 86/14 | 78 |
| 20 | **1j** | Xantphos | 7/93 | 94/6 | 79 |
| 21 | **1k** | BiPhePhos | 81/19 | 93/7 | 66 |
| 22 | **1k** | Xantphos | <5/>95 | >95/<5 | 72 |
| 23 | **1l** | BiPhePhos | | | nr |
| 24 | **1l** | Xantphos | | | nr |
| 25 | **1m** | BiPhePhos | 63/37 | 67/33 | 50 |
| 26 | **1m** | Xantphos | 6/94 | 92/8 | 73 |
| 27 | **1n** | BiPhePhos | 73/27 | 82/18 | 69 |
| 28 | **1n** | Xantphos | 25/75 | 79/21 | 74 |
| 29 | **1o** | BiPhePhos | 57/43 | 43/57 | 43 |
| 30 | **1o** | Xantphos | 25/75 | 74/26 | 54 |
| 31 | **1p** | BiPhePhos | 75/25 | 80/20 | 62 |
| 32 | **1p** | Xantphos | 62/38 | 91/9 | 79 |
| 33 | **1q** | BiPhePhos | >95/<5 | 72/28 | 47[d] |
| 34 | **1q** | Xantphos | >95/<5 | 89/11 | 61[d] |

[a]$Rh(CO)_2(acac)$ (2 mol %), ligand (6 mol %), **1a** (1 equiv, 0.03 mol·$L^{-1}$), $CO/H_2$ (1:1, 5 bar with Xantphos and 1:5, 10 bar with BiPhePhos), toluene, 70 °C, 16 h. Ratios determined by $^1H$ NMR analysis of the crude. [b]Isolated yield of **2** + **3**. [c]Only **3e** has been isolated. [d]Conversion = 70%.



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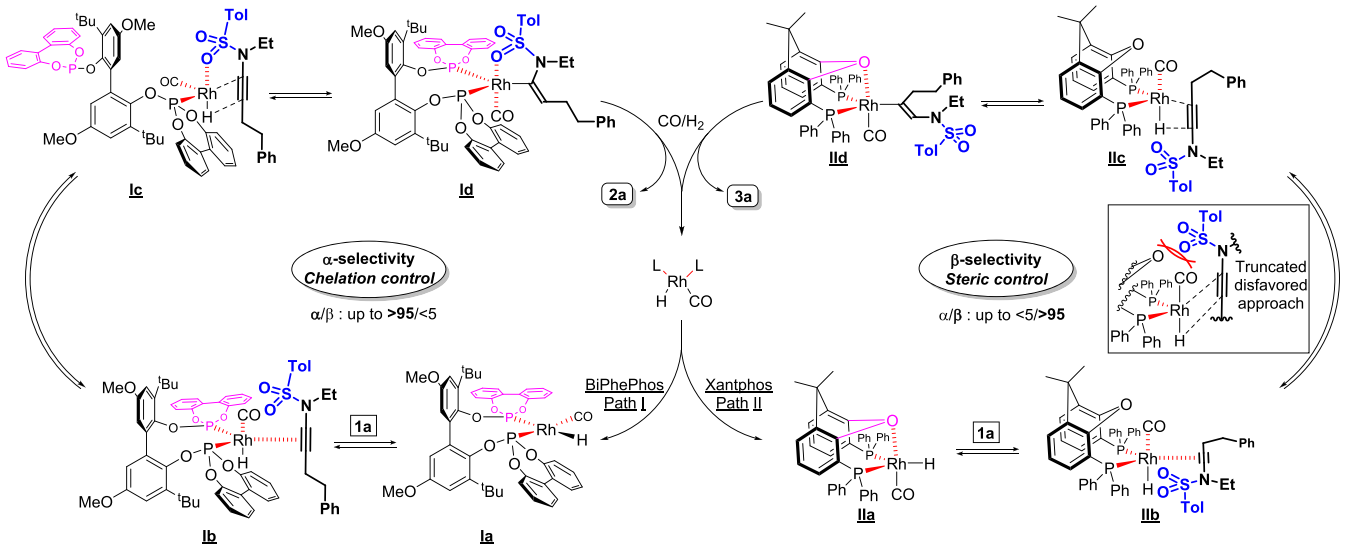


**Figure 2.** Hypothesis about the control of regioselectivity depending on the type of ligand used.

the steric hindrance around the alkyne has a dramatic effect on the conversion of the reaction as, in both cases (**1d** and **1l**), the starting material was fully recovered after 16 h.

The presence of an additional chelating moiety on the nitrogen side such as morpholine (**1m**) induced a slight decrease of the selectivity when BiPhePhos was used as ligand, but notably the amount of reduced compound **4m** was significantly increased (entry 25). However, when the reaction was performed with Xantphos, the reaction proceed with results in the classical range of the previous substrates (entry 26).

Interestingly, the use of an amino acid derivative bearing a carboxyl group as a chelating group (**1n**) induced in equivalent proportion an increase of the regioselectivity (**2** vs **3**) with BiPhePhos (entry 27) and a decrease of it with Xantphos (entry 28). Remarkably, the latter was accompanied with an increase of the undesired reduction leading to **4n**.

Finally, the steric parameter in the $\beta$ position was investigated using the relatively low bulky oxazolidinone as nitrogen moiety. Logically, with BiPhePhos as the ligand, the major isomer is systematically the $\alpha$ one, with good to very good selectivity. The steric control of the regioselectivity with Xantphos as ligand has been demonstrated. Indeed, the more the steric congestion increases, the more the proportion of $\alpha$ isomer significantly increases ultimately going to a total inversion of the selectivity in the case of a *tert*-butyl group.

A possible explanation for the regioselectivity observed is based on the electronic richness of the phosphorus atom of the two families of ligands (Figure 2). In our opinion, the discriminating step is the hydrometalation one. In the case of phosphine ligands, the phosphorus is relatively electron-rich with a high $\sigma$-donating character[24] resulting in a coordination to the rhodium strong enough to avoid the competitive coordination of the sulfonamide moiety of the ynamide. In that case, only the polarization and the steric hindrance of the alkyne is influencing the selectivity (Int. **IIc**) by installing the rhodium at the most electron rich and the less hindered position, namely the $\beta$ one (Int. **IId**). Under these conditions, the 3-aminoacrolein **3a** is the major product of the reaction (Figure 2, path II).

Conversely, when the less $\sigma$-donating phosphite ligand is used,[10] the electron-withdrawing group can coordinate the rhodium center (Int. **Ic**) to install the catalyst at the $\alpha$ position through an 5-*exo*-*dig* type hydrometalation (Int. **Id**) resulting in the formation of enaminal **2a** as the major product (Figure 2, path I).

To conclude, we have developed a regiodivergent access to 2- and 3-amino acrolein derivatives based on the hydroformylation of ynamides. The stereospecificity is totally conserved as the reaction is always leading to the product resulting from the syn addition of the hydrogen and the formyl group on the alkyne moiety. The regioselectivity can be controlled by the ligand and can be inverted according to its nature. The use of BiPhePhos mainly furnishes the $\alpha$ isomer, while the use of Xantphos allows us to obtain quasi-exclusively the $\beta$ one. More broadly, this study opens the door to regiodivergent hydroformylations of alkynes. The concept used, i.e., chelation versus steric control, to access selectively one or the other regioisomer could be generalized and is under investigation in our laboratory. In addition, both experimental and in silico investigations are in progress to better rationalize the regioselectivity of the reaction.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03566.

Experimental procedures; full spectroscopic data for all new compounds; copies of $^{1}$H and $^{13}$C NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.



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