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Rhodium-Catalyzed Enantioselective Anti-Markovnikov Hydroformylation of α-Substituted Acryl Acid Derivatives

Shuailong Li, Zhuangxing Li, Cai You, Xiuxiu Li, Jiaxin Yang, Hui Lv,* and Xumu Zhang*

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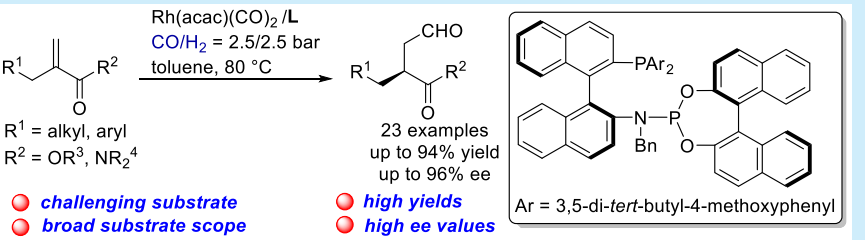

ABSTRACT: Rhodium-catalyzed asymmetric anti-Markovnikov hydroformylation of α-substituted acrylates/acrylamides has been developed. By employing the Rh/(*S*,*S*)-DTBM-YanPhos complex, a series of β-chiral linear aldehydes were obtained in high yields (up to 94% yield) and high enantioselectivities (up to 96% ee). The utility of this methodology is demonstrated by a gram-scale reaction and a concise synthetic route to chiral γ-butyrolactone.

Owing to the efficient formation of chiral aldehydes in an atom-economic manner, enantioselective hydroformylation has attracted great attention in both academia and industry, and a great deal of efforts have been made in this field.[1] As a result, a variety of privileged ligands for asymmetric hydroformylation (AHF) of monosubstituted and 1,2-disubstituted alkenes, such as Binaphos,[2] bis(diazaphospholane) (BDP),[3] YanPhos,[4] Ph-BPE,[5] Chiraphite,[6] Bobphos,[7] and Bettiphos,[8] have been developed, giving α-chiral aldehydes in good yields with high enantioselectivities, which have greatly promoted the development of asymmetric hydroformylation. However, most of these ligands were incapable of catalyzing 1,1-disubstituted alkenes to the corresponding β-chiral linear aldehydes (as indicated by Keulemans' empirical rule),[9] although they performed very well on AHF of monosubstituted and 1,2-disubstituted alkenes. To date, the investigations on AHF of 1,1-disubstituted alkenes are rather limited[10] due to the low reactivity derived from the steric hindrance standing on the same side of the double bond and the low enantioselectivity derived from the inability of the chiral catalyst to differentiate the two enantiotopic faces of the substrates.

In 2011, Buchwald and co-workers reported their pioneering work in Rh-catalyzed AHF of functionalized 1,1-disubstituted olefins and successfully synthesized a series of β-chiral linear aldehydes from α-alkyl acrylates by using a Rh/BenzP* catalytic system.[11] However, the substrate scope is limited, and only bulky α-branched alkyl-substituted acrylates can afford target products with high yields and high ee's (up to 91% yield, 94% ee); hence, the general and efficient asymmetric hydroformylation of 1,1-disubstituted olefins has been far less established.

With respect to asymmetric hydroformylation, our group is devoted to addressing some long-standing tough problems in AHF by the development of new chiral ligands. Recently, our group designed and synthesized a series of (*S*,*S*)-YanPhos, which showed high activity and selectivity on unfunctionalized 1,1-disubstituted alkenes.[4g,i] Given the very similar stereocontrol model, we believe that (*S*,*S*)-YanPhos may also have good performance in asymmetric hydroformylation of functionalized 1,1-disubstituted olefins, providing an efficient approach to 1,4-dicarbonyl compounds, which are widely occurring in biologically active molecules and active pharmaceutical ingredients (Figure 1).[12] With this thought in mind, we investigated the asymmetric hydroformylation of α-substituted acryl acid derivatives.

On the basis of previous studies, **1a** was chosen as the standard substrate to optimize reaction conditions (Table 1). Initially, several representative ligands in AHF and in the asymmetric hydrogenation area, such as (*S*)-BINAP, Xuphos, (*S*,*S*)-Me-Duphos, and Walphos, were tested (Figure 2). Disappointingly, all of them exhibited low activities in this transformation and afforded target product **2a** with low enantiomeric excess (ee). When (*S*)-Binapine was employed, only a racemic hydrogenation product was generated (entry 5).

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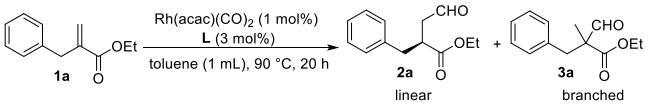
Table 1. Ligand Screening in the Asymmetric Hydroformylation of Ethyl 2-Benzylacrylate (1a)[a]



entry	ligand	CO/H_2 (bar)	conv. (%)[b] (%)[c]	2a:3a	ee (%)[d]
1	(*S*)-BINAP	5/5	11(3)	17:83	10(R)
2	Xuphos	5/5	6(5)	84:16	35
3	(*S*,*S*)-Me-Duphos	5/5	14(3)	22:78	53
4	Walphos	5/5	64(13)	28:72	55
5	(*S*)-Binapine	5/5	>99(0)	-	ND
6	(R_c,S_p)-Duanphos	5/5	>99(28)	31:69	76(R)
7	(*S*,*R*)-YanPhos	5/5	55(46)	81:19	20
8	(*S*,*S*)-YanPhos	5/5	>99(78)	97:3	54
9	(*S*,*S*)-DTB-YanPhos	5/5	>99(80)	97:3	86
10	(*S*,*S*)-DTBM-YanPhos	5/5	>99(84)	97:3	90
11	(*S*,*S*)-DTBM-YanPhos	2.5/2.5	>99(84)	97:3	90
12[e]	(*S*,*S*)-DTBM-YanPhos	2.5/2.5	88(85)	97:3	90
13[f]	(*S*,*S*)-DTBM-YanPhos	2.5/2.5	>99(94)(94)[g]	97:3	90

[a]Unless otherwise stated, all reactions were performed on a 0.2 mmol scale in 1 mL of toluene with substrate/Rh = 100 at 90 °C for 20 h. All temperatures in the text were the setting temperatures of the automatic heating control system, and the actual temperatures were changed within 0.5 °C of the setting temperatures. [b]Determined by ^{1}H NMR spectroscopy. [c]Yield of **2a** by ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis after a Wittig reaction. The absolute configuration was assigned by comparing the sign of the optical rotation of (*S*)-**2a** with that reported in the literature. See ref 1 in the Supporting Information. [e]*T* = 70 °C. [f]**L**/Rh = 2/1, 80 °C. [g]Isolated yield.

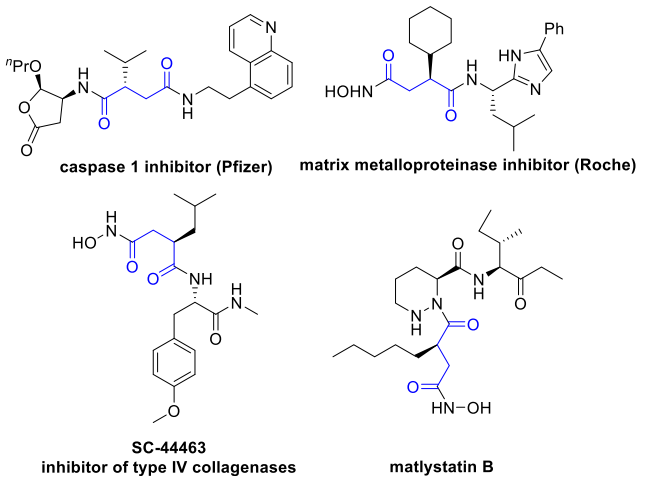


Figure 1. Biologically active compounds containing 1,4-dicarbonyl moieties.

(*Rc*,*Sp*)-Duanphos gave **2a** (entry 6, 76% ee) with good enantioselectivity along with a mass amount of branched aldehyde **3a**. (*S*,*R*)-YanPhos, which proved to be efficient on AHF of monosubstituted and 1,2-disubstituted alkenes, afforded **2a** in 46% yield with 20% ee as well as a spot of **3a** (entry 7). (*S*,*S*)-YanPhos which has excellent performance in AHF of unfunctionalized 1,1-disubstituted olefins was evaluated; to our delight, full conversion and moderate ee (entry 8, >99% conv., 54% ee) were obtained, and the fomation of **3a** was effectually inhibited simultaneously. Then, more bulky chiral ligands, such as (*S*,*S*)-DTB-YanPhos and (*S*,*S*)-DTBM-YanPhos, were tested, and the results indicated that the enantioselectivity was gradually improved with the increase of the steric hindrance on the phosphine atom of the ligand. Thus, the highest ee was obtained (entry 10, 90% ee) with (*S*,*S*)-DTBM-YanPhos, albeit with 3% branched aldehyde **3a**. Subsequently, the impact of temperature and the ratio of ligand to metal was evaluated (for more details on the

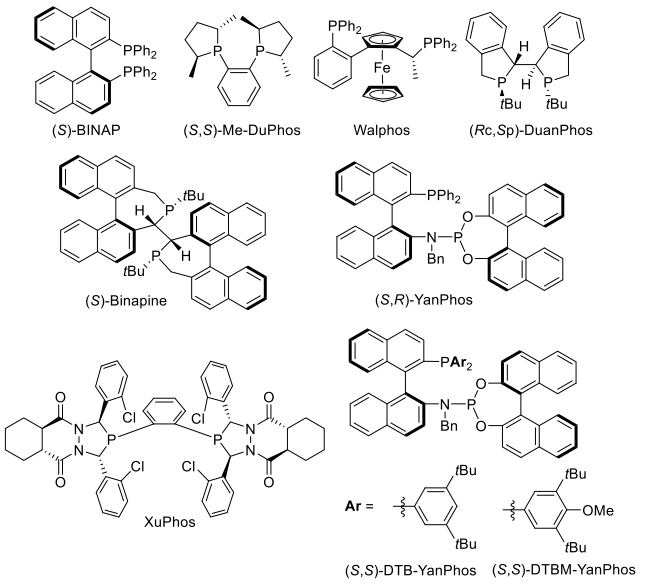


Figure 2. Structures of the evaluated ligands for asymmetric hydroformylation of **1a**.

condition optimization, see the ligand screening in Supporting Information), and the best result was obtained when the reaction was conducted at a lower temperature (80 °C) and lower ratio of ligand to metal (L/Rh = 2/1), giving **2a** with high isolated yield and excellent ee (entry 13, 94% isolated yield, 90% ee).

Under the optimized reaction conditions, we explored the substrate scope and tested the generality of this asymmetric transformation. In order to probe the effect of the ester group on this AHF reaction, a series of substrates containing different ester groups were investigated (Scheme 1). Linear aldehydes with β-chirality (**2a**, **2b**, **2c**, **2d**) were obtained with high yields and excellent ee's, and a slight trend emerged that the ee value increased slightly with the increase of ester group steric

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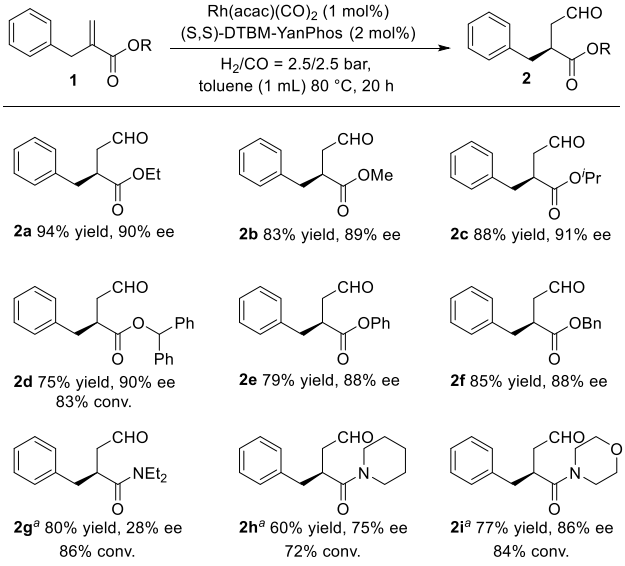
Scheme 1. Asymmetric Hydroformylation of α-Substituted Acrylates and Acrylamides*

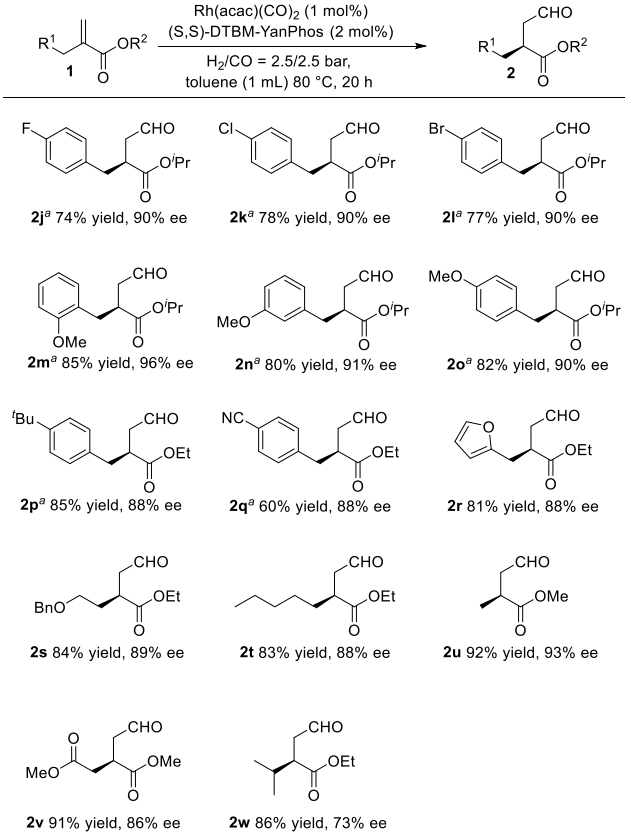


*Reaction conditions: **1** (0.2 mmol), $Rh(acac)(CO)_2$ (1 mol %), (*S*,*S*)-DTBM-YanPhos (2 mol %), CO (2.5 bar), H_2 (2.5 bar), toluene (1 mL), 80 °C, 20 h. Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. Isolated yields. [a]0.5 mL of toluene, 48 h.

hindrance. The steric hindrance of benzhydryl is too large, which might reduce the coordination ability of **1d** to rhodium, and the conversion was thus decreased to some extent. At the same time, phenyl acrylate and benzyl acrylate were transformed to **2e** and **2f** smoothly with high yields and good ee, respectively. However, acrylamides showed lower reactivity and enantioselectivity (**2g**). By changing the amide-protecting group and prolonging the reaction time, the corresponding aldehydes with β-chirality (**2h**, **2i**) were obtained with moderate to good yields and ee, respectively.

We then investigated the scope of the α-substituted acrylates (Scheme 2). When R^1 is an aryl group, a set of halogen atoms on the *para*-position of the benzene ring were compatible for this transformation to generated β-chiral aldehydes with good yield and high ee values (**2j**, **2k**, **2l**). For the substrates bearing an electron-donating group (OMe, *t*-Bu) on the benzene ring, the yields were increased slightly no matter the substituent position (**2m**, **2n**, **2o**, **2p**). In contrast, with an electron-withdrawing cyano group at the *para*-position on the benzene ring, **2q** was formed with a lower yield as partially hydrogenated byproduct was produced, but good ee was retained. Replacing R^1 with a heteroaryl group (2-furyl), the reaction worked very well (**2r**). Substrates containing either a benzyl ether group or an *n*-amyl were also successfully transformed to the corresponding chiral aldehydes (**2s**, **2t**). Commercially available α-methyl methacrylate and dimethyl itaconate proceeded smoothly in this reaction, offering the corresponding aldehydes with high yields and good ee (**2u**, **2v**). It is worth noting that the ee was decreased to some extent when α-branched acrylate was employed (**2w**). Compared with the best catalytic system reported previously for AHF of α-substituted acrylates,[11] this method exhibited better substrate generality as well as better performance in yield and in enantioselectivity except for AHF of α-branched acrylate **2w**.

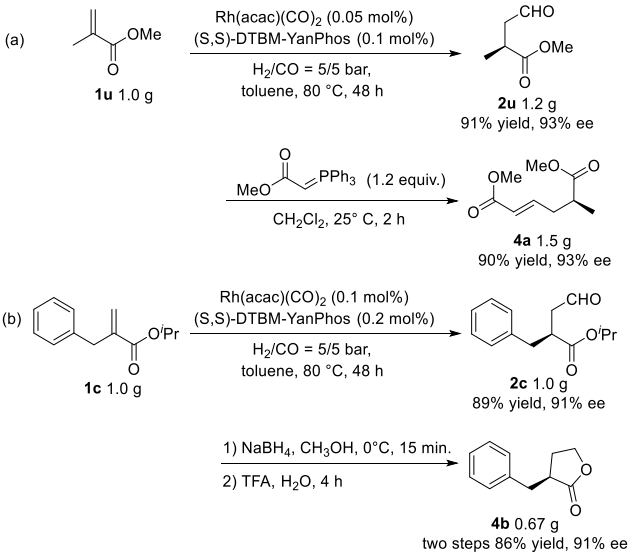
Scheme 2. Asymmetric Hydroformylation of α-Substituted Acrylates*



*Reaction conditions: **1** (0.2 mmol), $Rh(acac)(CO)_2$ (1 mol %), (*S*,*S*)-DTBM-YanPhos (2 mol %), CO (2.5 bar), H_2 (2.5 bar), toluene (1 mL), 80 °C, 20 h. Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. Isolated yields. [a]48 h.

With the scope of the transformation established, we sought to demonstrate the synthetic utility of the current methodology. As summarized in Scheme 3, a gram-scale AHF reaction

Scheme 3. Gram-Scale Asymmetric Hydroformylation and the Synthesis of Chiral γ-Butyrolactone



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of **1u** was conducted under the optimized condition with 0.05 mol % of catalyst loading, giving the target linear aldehyde (**2u**) in 91% yield without compromising the enantioselectivity. Remarkably, a one-pot hydroformylation/Wittig olefination sequence[13] was also compatible, furnishing the corresponding olefin **4a** with 90% yield and 93% ee. In addition, a concise synthetic route to γ-benzyl butyrolactone **4b** was also enabled by an efficient AHF of **1c**, followed by the reduction with $NaBH_4$ and intramolecular transesterification reaction.

In summary, a rhodium-catalyzed asymmetric hydroformylation of α-substituted acrylates and acrylamides has been developed, furnishing the corresponding β-chiral linear aldehydes with generally high yields and good enantioselectivities. Furthermore, the broad substrate scope, easy scale-up with a low catalyst loading, and versatile transformations of aldehyde guarantee wide application of this method in organic synthesis. Further investigations on asymmetric hydroformylation and related cascade reactions are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04624.

General Information; ligand screening in the asymmetric hydroformylation (AHF) of **1a**; general procedure for AHF; procedures for gram-scale AHF of **1u** and the synthesis of **4a**; procedures for gram-scale AHF of **1c** and the synthesis of **4b**; references; NMR spectra; and HPLC spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Hui Lv − *Wuhan University, Wuhan, China;* orcid.org/0000-0003-1378-1945; Email: huilv@whu.edu.cn

Xumu Zhang − *Southern University of Science and Technology, Shenzhen, China;* orcid.org/0000-0001-5700-0608; Email: zhangxm@sustc.edu.cn

Other Authors

Shuailong Li − *Wuhan University, Wuhan, China*
Zhuangxing Li − *Wuhan University, Wuhan, China*
Cai You − *Wuhan University, Wuhan, China*
Xiuxiu Li − *Wuhan University, Wuhan, China*
Jiaxin Yang − *Wuhan University, Wuhan, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.9b04624

Notes

The authors declare no competing financial interest.

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