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Enantioselective Rh-Catalyzed Anti-Markovnikov Hydroformylation of 1,1-Disubstituted Allylic Alcohols and Amines: An Efficient Route to Chiral Lactones and Lactams

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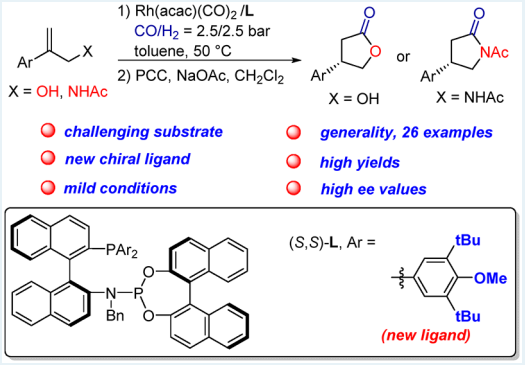
Supporting Information

ABSTRACT: Rh-catalyzed highly enantioselective anti-Markovnikov hydroformylation of 1,1-disubstituted allylic alcohols and amines has been achieved. By using a chiral hybrid phosphorus ligand, a series of challenging 1,1-disubstituted allylic alcohols and amines were transformed to valuable chiral lactones and lactams with good yields and high enantioselectivities (up to 90% yield and 93% enantiomeric excess (ee)) under very mild reaction conditions (50 °C, CO/H_2 = 2.5/2.5 bar). Furthermore, gram-scale reaction and diverse synthetic transformations have also been achieved, demonstrating the wide synthetic utility of this methodology.



KEYWORDS: *enantioselectivity, hydroformylation, rhodium, lactone, lactam*

Asymmetric hydroformylation (AHF) of alkenes represents an atom-economic route for the preparation of chiral aldehydes, which are important intermediates for drugs and synthetic chemicals.[1] Over the past decades, intensive efforts have been devoted to this field and a series of chiral phosphorus ligands, including Binaphos,[2] bis-(diazaphospholane) (BDP),[3] YanPhos,[4] Bobphos,[5] Ph-BPE,[6] Chiraphite,[7] and other chiral phosphorus ligands,[8] have been developed for this asymmetric transformation. Although practical levels of regioselectivity and enantioselectivity can be obtained in AHF of some alkenes, the substrate scope is still narrow and mainly limited to monosubstituted and 1,2-disubstituted olefins. Because the adverse effect of steric hindrance on C═C bond coordination with a metal center, 1,1-disubstituted alkenes generally show low reactivity in AHF. In addition, in contrast to AHF of monosubstituted and 1,2-disubstituted alkenes with the formation of α-chiral branched aldehydes, AHF of 1,1-disubstituted alkenes to furnish β-chiral linear aldehydes (as indicated by Keulemans' empirical rule)[9] has proven to be a great challenge, because of the poor enantioselectivity.[1g] To date, there have been only a few successful examples (>90% enantiomeric excess (ee)) on AHF of 1,1-disubstituted alkenes have been achieved.[8b,10] Thus, expansion of the substrate scope and widening of the application of asymmetric hydroformylation is very desirable.

In a synthetic sense, AHF of allylic alcohols and amines, followed by oxidation or reduction, provides a concise method to valuable lactones, lactams, furanidines, and pyrrolidines, which occur in many natural products and are common motifs in many biologically active compounds. However, AHF of allylic alcohols and amines has been rarely investigated, because of the challenge involved in controling the enantioselectvity. For example, in the AHF of allylic alcohols, the hydroxyl group was expected to benefit for the stereo-induction, because of the weak coordination with Rh. Nevertheless, the results of AHF of 1,2-disubstituted allylic alcohols,[1g,11] 1,1-disubstituted allylic alcohols (see the Supporting Information) and the structurally similar aliphatic alkenes under the same reaction conditions demostrate that the hydroxyl group was actually deleterious to enantioselectivity.[1g] The Nozaki group[12] and the Landis group[3b] have reported the Rh-catalyzed asymmetric hydroformylation of cinnamyl alcohol, respectively. Recently, our group has achieved the AHF of 1,2-disubstituted protected allylic amines.[4e] In contrast to the success in AHF of 1,2-

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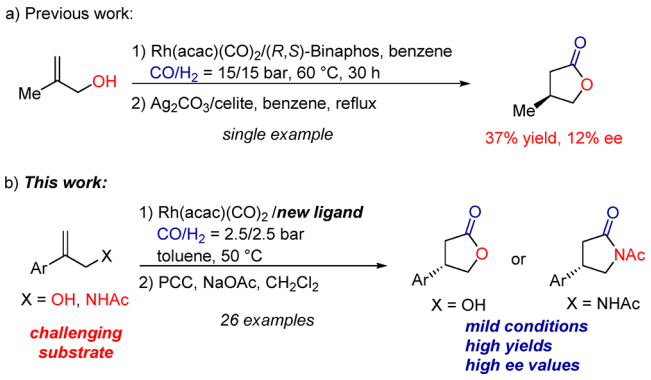
disubstituted allylic alcohols and amines, the results in AHF of 1,1-disubstituted allylic alcohols and amines seem lackluster. Because of the difficulty in controlling enantioselectivity and the inherently poor reactivity of 1,1-disubstituted allylic alcohols and amines, AHF of these substrates has been a challenge. In 1997, the Nozaki group reported the first but single example in AHF of 1,1-disubstituted allylic alcohols with only 12% ee and 37% yield (see Scheme 1a).[12] Herein, we

Scheme 1. Asymmetric Hydroformylation of 1,1-Disubstituted Allylic Alcohols and Amines



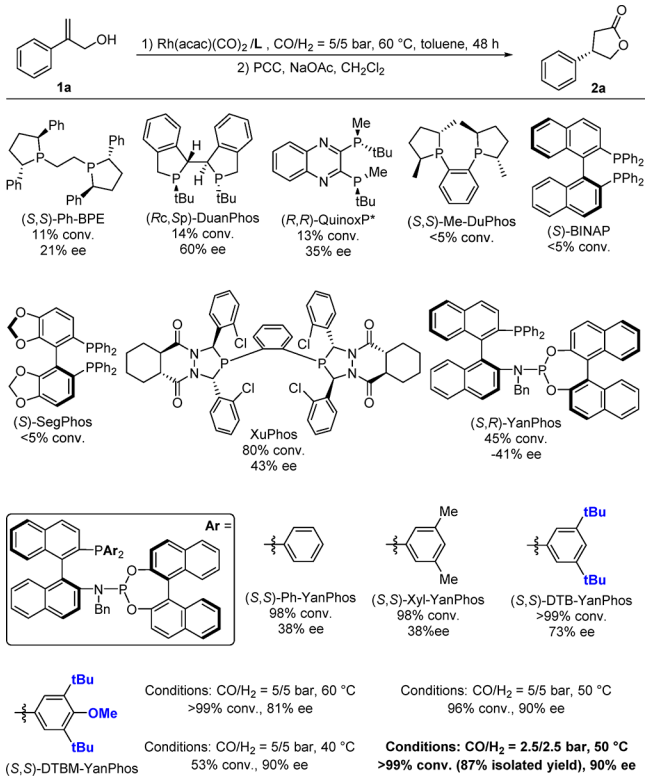
report the Rh-catalyzed AHF of the very challenging 1,1-disubstituted allylic alcohols and amines, and high yields (up to 95%) with good to excellent enantioselectivities (up to 93% ee) are achieved with our developed chiral ligand under very mild conditions (50 °C, CO/H_2 = 2.5/2.5 bar).

We initiated our studies by examining the asymmetric hydroformylation of the 1,1-disubstituted allylic alcohol **1** (Scheme 2). Chiral ligands that have good performance in the AHF or asymmetric hydrogenation (AH), such as (*S*,*S*)-Ph-BPE, (*Rc*,*Sp*)-DuanPhos, (*R*,*R*)-QuinoxP*, (*S*,*S*)-Me-DuPhos, (*S*)-BINAP, (*S*,*S*)-SegPhos, XuPhos, (*S*,*R*)-YanPhos, were tested, but the low conversions and low ee values revealed the dual challenges of achieving high levels of reactivity and enantioselectivity for 1,1-disubstituted allylic alcohols in asymmetric hydroformylation.

Next, we tested a series of (*S*,*S*)-YanPhos. (*S*,*S*)-Ph-YanPhos, and (*S*,*S*)-Xyl-YanPhos, which showed high conversions albeit with low ee values, which gave us a promising lead. By changing the *meta*-substituents on the phenyl group from methyl to *tert*-butyl ((*S*,*S*)-DTB-YanPhos), we obtained full conversion with 73% ee. We envisioned that further increasing the steric hindrance on the phosphine part of the ligand could improve the differentiation of the two prochiral faces of **1a**. To test this hypothesis, we prepared a novel analogue, (*S*,*S*)-DTBM-YanPhos, which bears an additional parathoxy substituent. To our delight, this ligand afforded full conversion with 81% ee. Subsequently, other reaction conditions, such as pressure and temperature, were evaluated. We found that lower reaction temperature led to higher enantioselectivity, albeit with lower conversion. Decreasing the syngas pressure resulted in higher conversion, and the enantioselectivity remained the same. Finally, the complete conversion was achieved under 5 bar CO/H_2 (1:1) at 50 °C, affording the desired product with full conversion (87% isolated yield) and 90% ee.

Under the optimal conditions, the substrate scope and generality of this reaction were evaluated. In most cases, the

Scheme 2. Evaluation of Chiral Ligands[a]



[a]Reaction conditions: **1a** (0.2 mmol), $Rh(acac)(CO)_2$ (4 mol %), ligand (12 mol %), CO (5 bar), H_2 (5 bar), toluene (1 mL), 60 °C, 48 h. Oxidation conditions: Pyridinium chlorochromate (PCC) (0.4 mmol), sodium acetate trihydrate (0.4 mmol), SiO_2 (100 mg), CH_2Cl_2 (5 mL), 25 °C, overnight. Conversions were determined by ^1H NMR analysis. Enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase.

1,1-disubstituted allylic alcohols could be transformed to the chiral lactones with high ee values and good to excellent yields (see Scheme 3). Various functional groups, such as methyl (**2b**), isopropyl (**2c**), tertiary butyl (**2d**) phenyl (**2e**), methoxyl (**2f**), trifluoromethyl (**2g**), esters (**2h**), and halides (**2i** and **2j**), at the *para* position of the phenyl group, were well-tolerated in this reaction. In addition, the substrate with *meta*-substitution on the phenyl group also worked smoothly, delivering target product with high ee value (**2k**). As the steric hindrance increased, substrate with a substitution on the *ortho* position of benzene ring showed slightly low reactivity, but high yield with high enantioselectivities were obtained at higher temperature (**2l**). Moreover, substrates with 3,4-disubstituted groups and 3,5-disubstituted groups could be accommodated, as exemplified by **2m**−**2o** and **2p**, respectively. Furthermore, naphthyl, furyl, benzofuryl and benzothienyl substrates were also compatible with this transformation, affording chiral lactones **2q**, **2r**, **2s**, and **2t** in good yields with high ee values.

Next, we investigated the Rh-catalyzed asymmetric hydroformylation of more-challenging 1,1-disubstituted allylic amines (Scheme 4). In contrast with the AHF of 1,1-disubstituted allylic alcohols, lower yields, and ee values were obtained in the AHF of these acetyl protected allylic amines, as summarized in Scheme 4. Even so, six valuable chiral lactams were obtained with good ee values, albeit with moderate yields. Moreover, we found that different substituents on the phenyl group, such as methyl (**4b**), methoxyl (**4c**), trifluoromethyl

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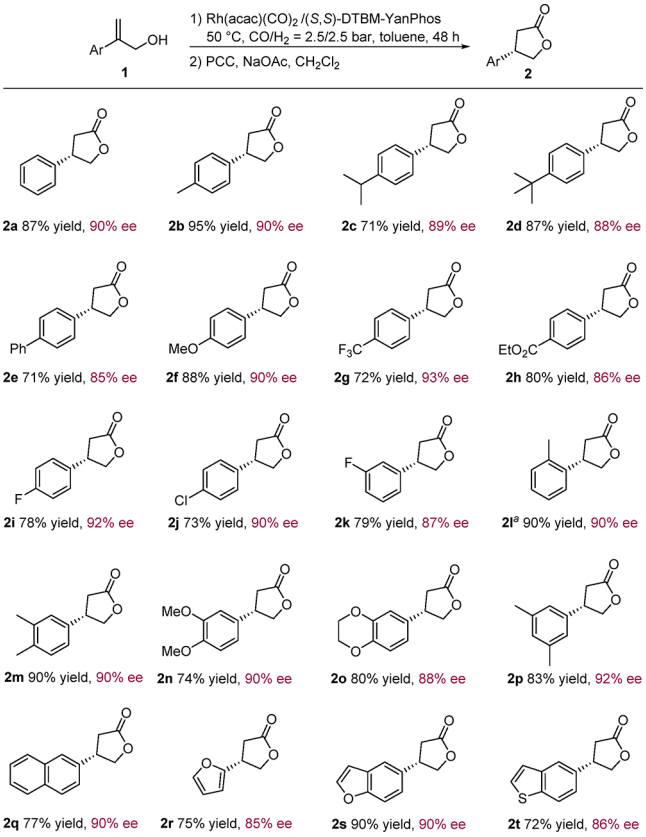
Scheme 3. Asymmetric Hydroformylation of 1,1-Disubstituted Allylic Alcohols*



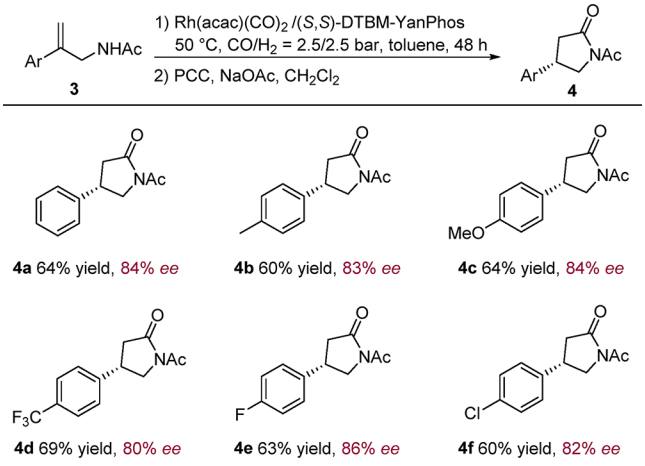
*Reaction conditions: **1** (0.2 mmol), $Rh(acac)(CO)_2$ (4 mol %), (*S*,*S*)-DTBM-YanPhos (12 mol %), CO (2.5 bar), H_2 (2.5 bar), toluene (1 mL), 50 °C, 48 h. Oxidation conditions: Pyridinium chlorochromate (PCC) (0.4 mmol), sodium acetate trihydrate (0.4 mmol), SiO_2 (100 mg), CH_2Cl_2 (5 mL), 25 °C, overnight. Isolated yields. Enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary. [a]70 °C, 72 h.

(**4d**), and halides (**4e** and **4f**), have a very small effect on yields and enantioselectivities in this transformation.

With the scope of the transformation established, we sought to demonstrate the potential utility of this protocol and several transformations were conducted, as summarized in Scheme 5. First, upon decreasing the catalyst loading to 1 mol %, the asymmetric reaction was conducted on a gram scale, affording the desired hemiacetal **5** in good yield with excellent enantioselectivity, albeit with a low diastereomeric ratio (dr) (Scheme 5a). The hemiacetal **5** was subsequently subjected to a series of useful organic transformations (Scheme 5b). Treatment of the hemiacetal **5** to PCC oxidation conditions provided the chiral lactone **2p** in 92% isolated yield with 90% ee. In addition, **5** was treated with triethylsilane and $BF_3{\cdot}OEt_2$ to furnish **6a** in good yield without any loss of enantiopurity. Also, 2,4-disubstituted furan **6b** was formed in high yield with high diastereoselectivity and enantioselectivity by the treatment of allyltrimethyl silane in the presence of $BF_3{\cdot}OEt_2$. Reduction of hemiacetal **5** with $NaBH_4$ yielded chiral diol **6c** in almost quantitative yield with 90% ee. Furthermore, starting from **2a** and **2j**, Phenibut[13] and Baclofen[14] can be synthesized readily, following published literature procedures.[15]

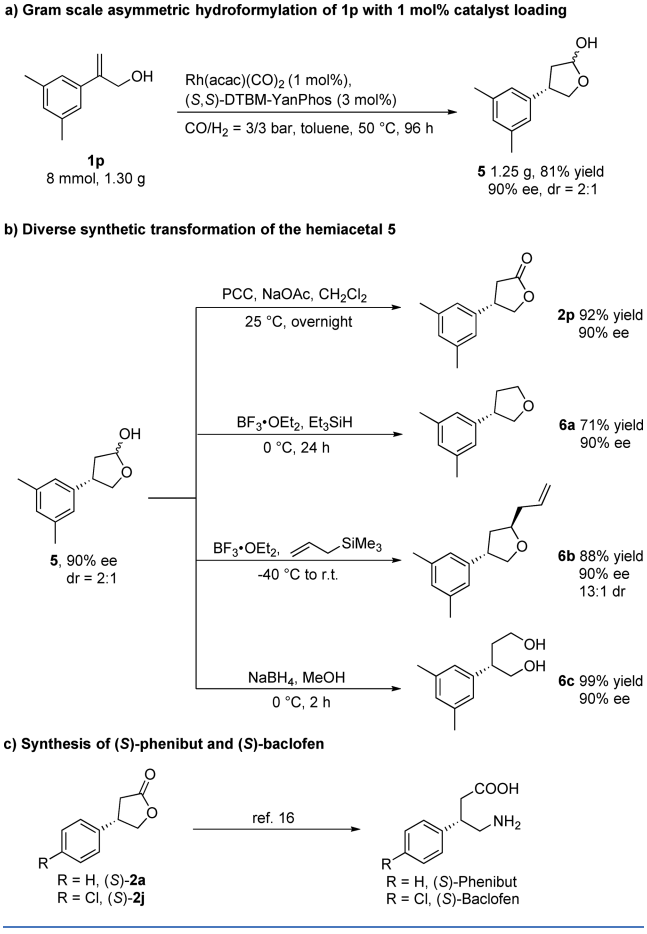
In summary, by employing our developed chiral hybrid phosphorus ligand (*S*,*S*)-DTBM-YanPhos, highly enantioselective Rh-catalyzed *anti*-Markovnikov hydroformylation of challenging 1,1-disubstituted allylic alcohols and amines was achieved under mild conditions and a wide range of chiral

Scheme 4. Asymmetric Hydroformylation of 1,1-Disubstituted Allylic Amines[a]



[a]Reaction conditions: **3** (0.2 mmol), $Rh(acac)(CO)_2$ (4 mol %), (*S*,*S*)-DTBM-YanPhos (12 mol %), CO (2.5 bar), H_2 (2.5 bar), toluene (1 mL), 50 °C, 48 h. Oxidation conditions: pyridinium chlorochromate (PCC) (0.4 mmol), sodium acetate trihydrate (0.4 mmol), SiO_2 (100 mg), CH_2Cl_2 (5 mL), 25 °C, overnight. Isolated yields. Enantiomeric excess (ee) values were determined by HPLC analysis using a chiral stationary.

Scheme 5. Synthetic Transformations



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lactones and lactams, which are important intermediates in organic synthesis, were obtained in good yields with high ee values. Furthermore, several synthetic transformations were conducted, demonstrating the high synthetic utility of the current reaction. The practicality of this asymmetric transformation was further enhanced by the gram-scale reaction. Further exploration into the chiral ligand design, substrate scope, mechanism, and applications of asymmetric hydroformylation is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.9b02667.

Experimental procedures and compound characterization (PDF)

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Notes

The authors declare no competing financial interest.

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