Stereospecific Hydroformylation of 1-Substituted Cyclopent-3-en-1-ols: A Concise Access to Bridged [2,2,1] Bicyclic Lactones With A Quaternary Stereocenter

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Abstract: An efficient method for enantioselective construction of bridged [2,2,1] bicyclic lactones bearing a quaternary stereocenter was achieved by Rh-catalyzed asymmetric hydroformylation /intramolecular cyclization/PCC oxidation. By employing a hybrid phosphine-phosphite chiral ligand, a series of cyclopent-3-en-1-ols were transformed into their corresponding γ-hydroxyl aldehydes with specific syn-selectivity, then hemiacetal formed in situ and oxidized by PCC in one-pot, affording bridged [2,2,1] bicyclic lactones in high yields and excellent enantiomeric excess. Replacing the hydroxyl group by an ester group, cyclopentanecarbaldehydes with a chiral all-carbon quaternary stereocenter in the γ-position can be generated efficiently. Gram-scale reaction and several transformations to corresponding amide, alcohol and acid demonstrated the practical value of this methodology.
Enantiomeric bridged [2,2,1] bicyclic lactones and their ring-open products, cyclopentanols bearing two chiral centers, are important scaffolds widely occurring in both pharmaceutics and biology active compounds (Figure 1).  Consequently, the synthesis of bridged[2,2,1] bicyclic lactones received wide attentions and several approaches have been developed. The typical methods including Baeyer-Villiger oxidation, esterification, halolactonization, electrocatalytic reaction and others. However, most of these approaches were focused on the synthesis of racemic bridged [2,2,1] bicyclic lactones and multi-step synthesis were necessary to achieve these transformations. To date, there are only two examples on the construction of chiral bridged [2,2,1] bicyclic lactones in an enantioselective manner. In 2015, Dominguez developed a new synthetic route to chiral bridged [2,2,1] bicyclic lactones by using chiral alcohol as starting material (Figure 2, a). In 2018, Zhu and co-workers developed a copper-catalyzed enantioselective arylative desymmetrization of prochiral cyclopentenes, and then followed by hydrolysis and intramolecular iodolactonlization to generate bridged [2,2,1] bicyclic lactones. However, the installation and removal of an amide direction group were essential to this synthetic route, which resulted in relatively low atom econmy (Figure 2, b). Therefore, the development of a concise and efficient method to produce bridged [2,2,1] bicyclic lactones is highly desirable.
Figure 1. Pharmaceutics and bioactive compounds containing bridged [2,2,1] bicyclic lactones and it’s alcohol derivatives.

Asymmetric hydroformylation (AHF) represents an efficient approach for asymmetric formation of C-C bond in an atomic economic manner,\textsuperscript{17, 18, 19, 20, 21, 22, 23, 24, 25} and the aldehyde products can be easily converted to versatile functional compounds, such as chiral alcohols, acids, amines and esters,\textsuperscript{26, 27, 28, 29, 30, 31, 32, 33, 34} thus asymmetric hydroformylation has been widely investigated and some significant progress have been made.\textsuperscript{35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45} However, asymmetric hydroformylation is very sensitive to the steric hindrance of substrate, which make it difficult to tolerate tri- or tetrasubstituted alkenes. As a result, the construction of chiral aldehydes with a quaternary stereocenter and a tertiary stereocenter by asymmetric hydroformylation is rarely exploited. To the best of our knowledge, there was only one report achieved this transformation by using desymmetric hydroformylation strategy, but the substrate scope was limited to cyclopropenes with high ring strain. Furthermore, only moderate to good enantioselectivities were obtained (≤ 83% ee).\textsuperscript{46} Consequently, highly efficient synthesis of multichiral aldehydes bearing a quaternary stereocenter is still a problematic issue in this field.

Recently, our group developed a Rh-catalyzed asymmetric hydroformylation of 1,1-disubstituted allyl alcohols to createc \( \gamma \)-butyrolactones.\textsuperscript{47} We envision that the similar transformation might occur if 1-substituted cyclopent-3-en-1-ols were used as starting material, providing efficient access to bridged [2,2,1] bicyclic lactones with a quaternary stereocenter. However, this transformation faces several challenges (Figure 2, c). First, it is very difficult to generate chiral aldehydes with exclusive syn-selectivity through asymmetric hydroformylation of 1-substituted cyclopent-3-en-1-ols, but it’s an essential factor to form bridged [2,2,1] bicyclic lactones in high yield. Second, the generation of the hemiacetals is unfavourable in this transformation because the large steric hindrance of tertiary alcohols greatly decreased the nucleophilic ability of hydroxy group to aldehydes. In addition, the relatively small steric difference between the two prochiral faces makes it difficult to obtain high enantioselectivity. Thus, the development of a highly efficient method for asymmetric synthesis of bridged [2,2,1] bicyclic lactones containing a quaternary stereocenter is still a challenge. Herein, we report one-pot synthesis of chiral bridged [2,2,1] bicyclic lactones from readily available cyclopent-3-en-1-ols.
a) Preparation of bridge[2,2,1]lactones from chiral alcohols

\[
\text{HO-} \quad \xrightarrow{\text{LHMDS, dioxane}} \quad \text{Ar} \\
\text{HO-} \quad \xrightarrow{\text{Br-}} \quad \text{Ar}
\]

b) Desymmetrization of prochiral cyclopentenes and iodolactonization to bridge[2,2,1]lactones

\[
\text{OMe} \quad \xrightarrow{\text{AsF}_6 \text{ Ph-I-Mes}} \quad \text{Cu(OTf)}_2 \\
\text{Cu(O8} \text{OF} \text{)}_2 \\
\text{bisoxazoline ligand} \\
2,6-di-terbutylpyridine \\
1) \text{NaOH/EtOH} \quad 50 \ ^\circ \text{C}, \ 12 \text{ h} \\
2) \text{I}_2/\text{KI}, \text{NaHCO}_3, \text{THF/H}_2\text{O}, \ 50 \ ^\circ \text{C} \quad \text{installation and removal of amide} \\
\text{direction group is essential}
\]

c) This work:

\[
\text{R} = \text{Aryl, alkyl} \\
\text{Synthesis of chiral aldehydes} \\
\text{CO/H}_2 \\
\text{PCC/NET}_3, \text{DCM} \\
r.t. \text{ overnight} \\
\text{X} \\
\text{Challenges:} \\
1) \text{Stereospecific formation of syn chiral aldehydes} \\
2) \text{The formation of hemiacetal is unfavorable due to the steric effect of tertiary alcohol} \\
3) \text{The relatively small steric difference make it difficult to differentiate the two prochiral faces}
\]

**Figure 2. Methods for synthesis of chiral bridged [2,2,1] bicyclic lactones:** (a), use chiral materials to build bridged [2,2,1] bicyclic lactones; (b), install a chiral center beforehand and iodolactonization to generate bridged [2,2,1] bicyclic lactones; (c), specific plane syn-selective hydroformylation and lactonization to form bridged [2,2,1] bicyclic lactones.

**Results**

**Reaction development and optimizations.** Initially, considering only syn oxo-products can be transferred to corresponding bridged [2,2,1] bicyclic lactones, asymmetric hydroformylation of 1a was investigated to obtain 2a stereospecifically. When (S,S)-Ph-BPE, the representative
ligand in AHF, was employed, \( \text{1a} \) was transformed into oxo-product with high conversion and excellent ee, along with good diastereoselectivity (table 1, entry 1). \((Rc,Sp)\)-Duanphos showed low activity in this transformation albeit with good stereocontrol (entry 2). \((R,R)\)-Quinoxp, which performed well in asymmetric hydrogenation reactions,\(^{49, 50, 51, 52, 53}\) afforded target product in low yield with moderate enantioselectivity (entry 3). The reaction was totally inhibited when \((S,S)\)-Me-Duphos and \((S)\)-Segphos were employed. In order to obtain higher enantio- and diastereoselectivity, a series of YanPhos with different axial chirality, which were developed by our group, were evaluated.\(^{54, 55, 56, 57}\) The results showed that all YanPhos type ligands had good catalytic activity for this transformation, but there were big differences in the control of enantioselectivity and diastereoselectivity. Generally, YanPhos containing \((S,R)\) axial chirality had better performance than that of YanPhos with \((S,S)\) axial chirality (entries 6-13). When \((S,R)\)-DM-YanPhos was employed (entry 11), the target product was obtained with the best diastereo- and enantioselectivity.

**Table 1. Ligand screening in the asymmetric hydroformylation of 1a**

| Entry | Ligand | Conv. (%)\(^{[b]}\) | Ee (%) of 3a\(^{[c]}\) | \((2a+2a')/2a''\) \(^{[b]}\) |
|-------|--------|-------------------|----------------|------------------|
| 1     | L1     | 90                | 94             | 12.5             |
| 2     | L2     | 43                | 90             | 5.3              |
| 3     | L3     | 37                | -73            | 2.9              |
| 4     | L4     | Trace             | ND             | ND               |
| 5     | L5     | Trace             | ND             | ND               |
| 6     | L6     | >99               | 45             | 4.2              |
| 7     | L7     | >99               | 50             | 5.3              |
| 8     | L8     | >99               | 79             | >20              |
| 9     | L9     | >99               | 70             | 7.7              |
The reaction of 1a (0.2 mmol) was performed in the presence of Rh(acac)(CO)$_2$ (2 mol%), L (4 mol%), H$_2$/CO = 5/5 bar in toluene (1 mL) at 70 ℃ for 24 h, then PCC (0.5 mmol) in DCM (4 mL) 25 ℃ for 12 h. After the completion of AHF, partial of reaction solution was took out for $^1$H NMR to detect the conversion of AHF and the ratio of $(2a+2a')/2a''$, the rest of solution was treated with PCC to give target product 3a.

[b] Determined by $^1$H NMR spectroscopy. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Isolated yield. ND = not detected.

**Figure 3.** Ligands evaluation for asymmetric hydroformylation of 1a.
Having established the optimized reaction condition for asymmetric hydroformylation of 1a, we attempt to synthesize bridged [2,2,1] bicyclic lactone 3a in one pot by sequential AHF / intramolecular cyclization / dehydrogenation oxidation (Table 2). Based on our previous work, PCC (pyridinium chlorochromate) was selected as oxidant and delivered target product 3a with moderate yield (entry 1). Increasing reaction temperature could not improve the yield (entry 2). Considering the bulky steric hindrance greatly decreased the nucleophilicity of tertiary alcohol, several additives were screened to promote the cyclization of 2a. Acetic acid lead to a significant drop in yield, NaOAc resulted in the decrease of yield to some extent. To our delight, K2CO3, Cs2CO3 and NEt3 can promote this reaction, affording target product in high yield without compromising the enantioselectivity (entries 5-7). However, a racemization occurred when NaOH was used, resulting in the decrease of ee and dr values (entry 8, 40% yield, 80% ee). Thus, one practical method for synthesis of bridged [2,2,1] bicyclic lactones was most effective with (S,R)-DM-YanPhos as the ligand in AHF and NEt3 as additive in PCC oxidation.

**Table 2 Additive screening in the PCC oxidation**[a]

| Entry | Additive      | Yield (%) | Ee (%) |
|-------|---------------|-----------|--------|
| 1     | -             | 61        | 94     |
| 2[c]  | -             | 56        | 94     |
| 3     | AcOH          | 26        | 94     |
| 4     | NaOAc•3H2O    | 49        | 94     |
| 5     | K2CO3         | 82        | 94     |
| 6     | Cs2CO3        | 85        | 94     |
| 7     | NEt3          | 90        | 94     |
| 8     | NaOH          | 40        | 80     |

[a]The reaction of 1a (0.2 mmol) was performed in the presence of Rh(acac)(CO)2 (2 mol%), L11 (4 mol%), H2/CO = 5/5 bar in toluene (1 mL) at 70 ℃ for 24 h, The reaction was cooled to room temperature and the pressure was carefully released in a well-ventilated hood, then the mixture was treated with PCC (0.5 mmol),
additive (0.1 mmol) in DCM (4 mL) 25 °C for 12 h in one pot. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Performed at 40 °C.

Under the optimal conditions, we investigated the substrate scope. All of the bridged [2,2,1] bicyclic lactones were prepared in good yields with excellent enantioselectivities (Figure 4). Substrates bearing halides on the phenyl ring performed well in this transformation, giving target products with high yields and excellent ee's (3b-3f). The absolute configuration of 3d was confirmed by X-ray crystallographic analysis. Electron-donating and electron-withdrawing substituted groups on the phenyl ring were also tolerated, furnishing 3f, 3g, 3h, 3i, 3j with high yields and excellent enantioselectivities, respectively. The yield of 3k was dropped sharply due to the ortho effect of methoxy group, but the high enantioselectivity was remained. In addition, functional groups, such as trifloromethyl, phenyl and borate (3l-3n) on the para-position of the benzene ring were compatible, and the corresponding products were afforded with moderate to good yields and high ee's. Replacing phenyl by a naphthyl group (3o), the reaction also proceeded smoothly, providing the desired compound with high yield and excellent ee. Notably, alkyl substituents, such as benzyl, n-hexyl, isopropyl, cyclopropyl, cyclopentyl and cyclohexyl were also well tolerated in this transformation, delivering bridged [2,2,1] bicyclic lactones with excellent ee's and high yields (3p-3u). Cyclopent-3-en-1-ol bearing a bulky sterically hindered damantyl group also proceeded effectively, affording target product with high yield (3v). Moreover, the oxo-product 2w was produced with high diastereoselectivity and excellent enantioselectivity. [60] Interestingly, 1-phenylcyclohept-4-en-1-ol, a challenge substrate for AHF because of the substituent far away from reaction site, which made it difficult to control the stereoselectivity, also worked very well in this transformation, delivering 6-oxabicyclo[3.2.2]nonan-7-one 3x with high yield and good enantioselectivity.
Figure 4. Scope of 1-substituted cyclopent-3-en-1-ols and 1-phenylcyclohept-4-en-1-ol.
Encouraged by the success of desymmetric strategy for construction of chiral bridged [2,2,1] bicyclic lactones with a O-substituted quaternary center, primary exploration on efficient synthesis of cyclopentanecarbaldehyde with an all-carbon quaternary stereocenter was conducted. As shown in Figure 5, when symmetric cyclopentene with phenyl and ester substituents was employed, the desired chiral aldehyde 5a was generated in good yield with high diastereo- and enantioselectivity. Moreover, all-carbon substituted chiral spiro-lactones could also be efficiently synthesized by this strategy, delivering target products with good yields and high enantioselectivities (5b, 5c).

![Diagram](image-url)

**Figure 5.** Substrates for synthesis of chiral aldehydes with an all-carbon quaternary stereocenter. The dr value of 5a-5c were determined by $^1$H NMR spectroscopy.

To further demonstrate the practical utility of this methodology, a gram-scale reaction of 1d were conducted in the presence of 0.2 mol% catalyst under 3/3 bar syngas pressure at 70 °C for 72 hours, then treated with NEt$_3$ and PCC, 3d was generated with high yield, without any loss in enantioselectivity (Figure 6, a). Treating 3d with methanol solution of ammonia, the ring-open reaction occurred, furnishing chiral amide 6 with high yield and excellent ee (Figure 6, b). The hydroformylation product 2a can be efficiently reduced by NaBH$_4$, affording chiral dual alcohol 7 in high yield (Figure 6, c). Under a mild condition, the bioactive chiral acid 8 was readily prepared by oxidation of 2m with H$_2$O$_2$ and NaClO$_2$ (Figure 6, d).
Figure 6. Gram-scale reaction and transformations of oxo-products and ring-open reaction of bridged [2,2,1] bicyclic lactones.

Conclusions

In summary, we have developed an efficient method for synthesizing bridged [2,2,1] bicyclic lactones bearing a quaternary stereocenter by one-pot sequential asymmetric hydroformylation/intramolecular cyclization/PCC oxidation. This methodology showed excellent substrate compatibility and excellent stereocontrol, giving target products with high yields and excellent enantioselectivities. In addition, this protocol also provided a useful strategy for construction of chiral aldehydes with an all-carbon quaternary stereocenter. Gram-scale reaction and diverse transformations of the oxo-products and bridged [2,2,1] bicyclic lactones demonstrated the utility of this method in synthetic chemistry. Further exploration on the construction of quaternary chiral center by asymmetric hydroformylation is ongoing in our laboratory.
Methods
See the Supplementary Methods for experimental details as well as characterization data, supplementary item 4-8 for the results of functional group tolerance of reactions for the results of additional reactions. NMR and HPLC spectra can be found in the Supplementary Information.

General procedure for Rh-catalyzed hydroformylation of 1-substituted cyclopent-3-en-1-olc and PCC oxidation. In a glovebox filled with argon, to a 5 mL vial equipped with a magnetic bar was added (S,R)-DM-YanPhos (0.004 mmol) and Rh(acac)(CO)$_2$ (0.002 mmol in 1 mL toluene). After stirring for 10 minutes, the mixture was charged to substrate (0.2 mmol). The vial was transferred into an autoclave and taken out of the glovebox. The argon gas was replacement with hydrogen gas for three times, and then hydrogen (2.5 bar) and carbon monoxide (2.5 bar) were charged in sequence. The reaction mixture was stirred at 70 °C (oil bath) for 48 h. The reaction was cooled to room temperature and the pressure was carefully released in a well-ventilated hood. The solution was transferred into a solution of pyridinium chlorochromate (PCC) (0.5 mmol) and triethylamine (0.1 mmol) in 4 mL dichloromethane, the reaction mixture was stirred at 25 °C (oil bath) overnight. The solution was concentrated and the product was isolated by column chromatography using petrol ether/EtOAc (30:1-10:1) as eluent to give the desired product. The enantiomeric excesses of 3a-3p, 3x, 5a-5c, 6, and 8 were determined by HPLC analysis using a chiral stationary phase. The enantiomeric excesses of 3q-3u, 2w and 7 were determined by SHIMADZU gas chromatography using chiral capillary columns.

And the racemate bridged [2,2,1] bicyclic lactones were prepared with PPh$_3$ as the ligand according to the general procedure described below: In a glovebox filled with argon, to a 5 mL vial equipped with a magnetic bar was added PPh$_3$ (0.004 mmol) and Rh(acac)(CO)$_2$ (0.002 mmol in 1 mL toluene). After stirring for 10 minutes, the mixture was charged to substrate (0.2 mmol). The vial was transferred into an autoclave and taken out of the glovebox. The argon gas was replacement with hydrogen gas for three times, and then hydrogen (10 bar) and carbon monoxide (10 bar) were charged in sequence. The reaction mixture was stirred at 110 °C (oil
bath) for 24 h. The reaction was cooled to room temperature and the pressure was carefully released in a well-ventilated hood. The solution was transferred into a solution of pyridinium chlorochromate (PCC) (0.5 mmol) and triethylamine (0.1 mmol) in 4 mL dichloromethane, the reaction mixture was stirred at 25 °C (oil bath) overnight. The solution was concentrated and the product was isolated by column chromatography using petrol ether/EtOAc (30:1-10:1) as eluent to give the desired product.

**Measurement of enantiomeric excess (ee).** The ee value was determined by chiral HPLC (CHIRALPAK AD-H and AS-H and CHIRALCEL OD-H and OJ-H column) and chiral GC (β-dex225).

**Data availability.** Crystallographic data for the structure 3d reported in this paper have been deposited at the Cambridge Crystallographic Data Centre under deposition number CCDC 2034549. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. All other data supporting the findings of this study, including experimental procedures and compound characterization, are available within the paper and its Supplementary Information, or from the corresponding author upon reasonable request.

**Author contributions**

H. L. and X.Z. directed the project. S. L. and H. L. contributed to the concept and design of the experiments. S. L., Z. L., M. L. and L. H. performed the experiments and data analysis. S. L. wrote the manuscript with feedback and guidance from H. L. and X.Z. All authors discussed the experimental results and commented on the manuscript.

**Additional information**

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at
www.nature.com/reprints. Correspondence and requests for materials should be addressed to H. L. or to X. Z.

Competing financial interests

The authors declare no competing financial or non-financial interests.

References

1. Xie L, Guo H-F, Lu H, Zhang X-M, Zhang A-M, Wu G, Ruan J-X, Zhou T, Yu D, Qian K, Lee K-H, Jiang S. Development and Preclinical Studies of Broad-Spectrum Anti-HIV Agent (3'R,4'R)-3-Cyanomethyl-4-methyl-3',4'-di-O-(S)-camphanoyl-(+)-cis-khellactone (3-Cyanomethyl-4-methyl-DCK). J. Med. Chem. 51, 7689-7696 (2008).

2. Xie L, Allaway G, Wild C, Kilgore N, Lee K-H. Anti-AIDS Agents. Part 47: Synthesis and Anti-HIV Activity of 3'-Substituted 3',4'-Di-O-(S)-camphanoyl-(3'R,4'R)-(+-) cis-khellactone Derivatives. Bioorg. Med. Chem. Lett. 11, 2291-2293 (2001).

3. Patterson B D, Lu Q, Aggen J B, Dozzo P, Kasar R A, Linsell M S, Kane T R, Gliedt M J, Hildebrandt D J, Mcenroe G A, Cohen F. World patent WO2013170030 (2013).

4. Brubaker J D, Dipietro L V. World patent WO2018022761 (2018).

5. Zhuang X-M, Deng J-T, Li H, Kong W-L, Ruan J-X, Xie L. Metabolism of novel anti-HIV agent 3-cyanomethyl-4-methyl-DCK by human liver microsomes and recombinant CYP enzymes. Acta. Pharmacol. Sin. 32, 1276-1284 (2011).

6. Yadav J S, Reddy B V S, Basak A K, Narsaiah A V. Baeyer-Villiger Oxidations in Ionic Liquids. A Facile Conversion of Ketones to Esters and Lactones. Chem. Lett. 33, 248-249 (2004).

7. Johansson P O, Bäck M, Kvarnström I, Jansson K, Vrang L, Hamelink E, Hallberg A, Rosenquist Å, Samuelsson B. Potent inhibitors of the hepatitis C virus NS3 protease: Use of a novel P2 cyclopentane-derived template. Bioorg. Med. Chem. 14, 5136-5151 (2006).

8. Bindra J S, Grodski A, Schaaf T K, Corey E J. New Extensions of the Bicyclo[2.2.1]heptane Route to Prostaglandins. J. Am. Chem. Soc. 95, 7522-7523 (1973).

9. Oppolzer W, Cunningham A F. Total synthesis of (±)chokol-A via an intramolecular type-I-magnesium ene reaction. Tetrahedron Lett. 27, 5467-5470 (1986).

10. Lomba L, Afarinika K, Vinader V. A new route to tricyclane sesquiterpenoids: total synthesis of α-ekasantalic acid. Org. Biomol. Chem. 17, 4456-4459 (2019).

11. Batanero B, Recio J, Barba F. One-pot anodic lactonization of Fenchone and Menthone and electrosynthesis of a new magnolione analogue. Electrochem. Commun. 66, 29-33 (2016).

12. Zhang A, Nie J. Enantioselective Synthesis of the Female Sex Pheromone of the Pink Hibiscus Mealybug, Maconellicoccus hirsutus. J. Agric. Food Chem. 53, 2451-2455 (2005).
13. Zhang A, Nie J, Khrimian A. Chiral synthesis of maconelliol: a novel cyclobutanoid terpene alcohol from pink hibiscus mealybug, Maconellicoccus hirsutus. *Tetrahedron Lett.* **45**, 9401-9403 (2004).

14. Hizuka M, Fang C, Suemune H, Sakai K. A Stereocontrolled Synthesis of Trisubstituted Cyclohexanes and Cyclopanetanes. Its Application to the Synthesis of 11-Deoxyprostaglandins *Chem. Pharm. Bull.* **37**, 1185-1187 (1989).

15. Penrose S D, Stott A J, Breccia P, Haughan A F, Bü rli R W, Jarvis R E, Dominguez C. Inter- and Intramolecular Annulation Strategies to a Cyclopentanone Building Block Containing an All-Carbon Quaternary Stereogenic Center. *Org. Lett.* **17**, 1401-1404 (2015).

16. Wu H, Wang Q, Zhu J. Copper-Catalyzed Enantioselective Arylative Desymmetrization of Prochiral Cyclopentenes with Diaryliodonium Salts. *Angew. Chem. Int. Ed.* **57**, 2721-2725 (2018).

17. Agbossou F, Carpentier J-F, Mortreux A. Asymmetric Hydroformylation. *Chem. Rev.* **95**, 2485-2506 (1995).

18. Breit B, Seiche W. Recent Advances on Chemo-, Regio- and Stereoselective Hydroformylation. *Synthesis.* **1**, 1-36 (2001).

19. Klosin J, Landis C R. Ligands for Practical Rhodium-Catalyzed Asymmetric Hydroformylation. *Acc. Chem. Res.* **40**, 1251-1259 (2007).

20. Franke R, Selent D, Börner A. Applied Hydroformylation. *Chem. Rev.* **112**, 5675-5732 (2012).

21. Jia X, Wang Z, Xia C, Ding K. Recent Advances in Rh-Catalyzed Asymmetric Hydroformylation of Olefins. *Chin. J. Org. Chem.* **33**, 1369-1381 (2013).

22. Chikkali S H, van der Vlugt J I, Reek J N H. Hybrid diphosphorus ligands in rhodium catalysed asymmetric hydroformylation. *Coord. Chem. Rev.* **262**, 1-15 (2014).

23. Deng Y, Wang H, Sun Y, Wang X. Principles and Applications of Enantioselective Hydroformylation of Terminal Disubstituted Alkenes. *ACS Catal.* **5**, 6828-6837 (2015).

24. Brezny A C, Landis C R. Recent Developments in the Scope, Practicality, and Mechanistic Understanding of Enantioselective Hydroformylation. *Acc. Chem. Res.* **51**, 2344-2354 (2018).

25. Li S, Li Z, You C, Lv H, Zhang X. Recent Advances in Asymmetric Hydroformylation. *Chin. J. Org. Chem.* **39**, 1568-1582 (2019).

26. Zhang X, Cao B, Yu S, Zhang X. Rhodium-Catalyzed Asymmetric Hydroformylation of N-Allylamides: Highly Enantioselective Approach to β3-Amino Aldehydes. *Angew. Chem., Int. Ed.* **49**, 4047-4050 (2010).

27. You C, Wei B, Li X, Yang Y, Liu Y, Lv H, Zhang X. Rhodium-Catalyzed Desymmetrization by Hydroformylation of Cyclopentenes: Synthesis of Chiral Carbocyclic Nucleosides. *Angew. Chem., Int. Ed.* **55**, 6511-6514 (2016).

28. Tanaka R, Nakano K, Nozaki K. Synthesis of α-Heteroarylpropanoic Acid via Asymmetric Hydroformylation Catalyzed by Rh(I)-(R,S)-BINAPHOS and the Subsequent Oxidation. *J. Org. Chem.* **72**, 8671-8676 (2007).

29. Zhang X, Cao B, Liu T-L, Zhang X. Rhodium-Catalyzed Asymmetric Hydroformylation of 1,1-Disubstituted Allylphthalimides: A Catalytic Route to β3-Amino Acids. *Adv. Synth. Catal.* **355**, 679-684 (2013).
30. Worthy A D, Joe C L, Lightburn T E, Tan K L. Application of a Chiral Scaffolding Ligand in Catalytic Enantioselective Hydroformylation. J. Am. Chem. Soc. 132, 14757-14759 (2010).
31. Joe C L, Blaisdell T P, Geoghan A F, Tan K L. Distal-Selective Hydroformylation using Scaffolding Catalysis. J. Am. Chem. Soc. 136, 8556-8559 (2014).
32. You C, Li X, Yang Y, Yang Y-S, Tan X, Li S, Wei B, Lv H, Chung L-W, Zhang X. Silicon-oriented regio- and enantioselective rhodium-catalyzed hydroformylation. Nat. Commun. 9, 2045 (2018).
33. Wong G W, Landis C R. Iterative Asymmetric Hydroformylation/Wittig Olefination Sequence. Angew. Chem., Int. Ed. 52, 1564-1567 (2013).
34. Li S, Li Z, You C, Li X, Yang J, Lv H, Zhang X. Rhodium-Catalyzed Enantioselective Anti-Markovnikov Hydroformylation of α-Substituted Acryl Acid Derivatives. Org. Lett. 22, 1108-1112 (2020).
35. Sakai N, Mano S, Nozaki K, Takaya H. Highly enantioselective hydroformylation of olefins catalyzed by new phosphine phosphite-rhodium(I) complexes. J. Am. Chem. Soc. 115, 7033-7034 (1993).
36. Noonan G M, Fuentes J A, Cobley C J, Clarke M L. An Asymmetric Hydroformylation Catalyst that Delivers Branched Aldehydes from Alkyl Alkenes. Angew. Chem. Int. Ed. 51, 2477-2480 (2012).
37. Babin J E, Whiteker G T. World patent WO1993003839 (1993).
38. Zhao B, Peng X, Wang Z, Xia C, Ding K. Modular Chiral Bidentate Phosphonites: Design, Synthesis, and Application in Catalytic Asymmetric Hydroformylation Reactions. Chem. Eur. J. 14, 7847-7857 (2008).
39. Peng X, Wang Z, Xia C, Ding K. Ferrocene-based bidentate phosphonite ligands for rhodium(I)-catalyzed enantioselective hydroformylation. Tetrahedron Lett. 49, 4862-4864 (2008).
40. Kuil M, Goudriaan P E, van Leeuwen P W N M, Reek J N H. Template-induced formation of heterobidentate ligands and their application in the asymmetric hydroformylation of styrene. Chem. Commun. 45, 4679-4681 (2006).
41. Tan R, Zheng X, Qu B, Sader C A, Fandrick K R, Senanayake C H, Zhang X. Tunable P-Chiral Bisdihydrobenzooxaphosphole Ligands for Enantioselective Hydroformylation. Org. Lett. 18, 3346-3349 (2016).
42. Schmitz C, Holthusen K, Leitner W, Franció G. Highly Regio- and Enantioselective Hydroformylation of Vinyl Esters Using Bidentate Phosphine-P-Chiral Phosphorodiamidite Ligands. ACS Catal. 6, 1584-1589 (2016).
43. Breeden S, Cole-Hamilton D J, Foster D F, Schwarz G J, Wills M. Rhodium-Mediated Asymmetric Hydroformylation with a Novel Bis(diazaphospholidine) Ligand. Angew. Chem., Int. Ed. 39, 4106-4108 (2000).
44. Hua Z, Vassar V C, Choi H, Ojima I. New biphenol-based, fine-tunable monodentate phosphoramidite ligands for catalytic asymmetric transformations. Proc. Natl. Acad. Sci. U. S. A. 101, 5411-5416 (2004).
45. Wang X, Buchwald S L. Rh-Catalyzed Asymmetric Hydroformylation of Functionalized 1,1-Disubstituted Olefins. J. Am. Chem. Soc. 133, 19080-19083 (2011).
46. Sherrill W M, Rubin M. Rhodium-Catalyzed Hydroformylation of Cyclopropenes. *J. Am. Chem. Soc.* **130**, 13804-13809 (2008).

47. You C, Li S, Li X, Lv H, Zhang X. Enantioselective Rh-Catalyzed Anti-Markovnikov Hydroformylation of 1,1-Disubstituted Allylic Alcohols and Amines: An Efficient Route to Chiral Lactones and Lactams. *ACS Catal.* **9**, 8529-8533 (2019).

48. Axtell A T, Cobley C J, Klosin J, Whiteker G T, Zanotti-Gerosa A, Abboud K A. Highly Regio- and Enantioselective Asymmetric Hydroformylation of Olefins Mediated by 2,5-Disubstituted Phospholane Ligands. *Angew. Chem. Int. Ed.* **44**, 5834-5838 (2005).

49. Li B, Chen J, Zhang Z, Gridnev I D, Zhang W. Nickel-Catalyzed Asymmetric Hydrogenation of N-Sulfonyl Imines. *Angew. Chem. Int. Ed.* **58**, 7329-7334 (2019).

50. Llopis Q, Guillamot G, Phansavath P, Ratovelomanana-Vidal V. Enantioselective Synthesis of α-Acetal-β'-Amino Ketone Derivatives by Rhodium-Catalyzed Asymmetric Hydrogenation. *Org. Lett.* **19**, 6428-6431 (2017).

51. Hu Q, Chen J, Zhang Z, Liu Y, Zhang W. Rh-Catalyzed One-Pot Sequential Asymmetric Hydrogenation of α-Dehydroamino Ketones for the Synthesis of Chiral Cyclic trans-β-Amino Alcohols. *Org. Lett.* **18**, 1290-1293 (2016).

52. Zhang Z, Tamura K, Mayama D, Sugiyama M, Imamoto T. Three-Hindered Quadrant Phosphine Ligands with an Aromatic Ring Backbone for the Rhodium-Catalyzed Asymmetric Hydrogenation of Functionalized Alkenes. *J. Org. Chem.* **77**, 4184-4188 (2012).

53. Ma M, Hou G, Wang J, Zhang X. Rhodium-catalyzed asymmetric hydrogenation of β-acetylamino acrylonitriles. *Tetrahedron: Asymmetry.* **22**, 506-511 (2011).

54. Yan Y, Zhang X. A Hybrid Phosphorus Ligand for Highly Enantioselective Asymmetric Hydroformylation. *J. Am. Chem. Soc.* **128**, 7198-7202 (2006).

55. Zhang X, Cao B, Yan Y, Yu S, Ji B, Zhang X. Synthesis and Application of Modular Phosphine-Phosphoramidite Ligands in Asymmetric Hydroformylation: Structure-Selectivity Relationship. *Chem. Eur. J.* **16**, 871-877 (2010).

56. Wei B, Chen C, You C, Lv H, Zhang X. Efficient synthesis of (S,R)-Bn-Yanphos and Rh/(S,R)-Bn-Yanphos catalyzed asymmetric hydroformylation of vinyl heteroarenes. *Org. Chem. Front.* **4**, 288-291 (2017).

57. You C, Li S, Li X, Lan J, Yang Y, Chung L W, Lv H, Zhang X. Design and Application of Hybrid Phosphorus Ligands for Enantioselective Rh-Catalyzed Anti-Markovnikov Hydroformylation of Unfunctionalized 1,1-Disubstituted Alkenes. *J. Am. Chem. Soc.* **140**, 4977-4981 (2018).

58. Chen C, Jin S, Zhang Z, Wei B, Wang H, Zhang K, Lv H, Dong X-Q, Zhang X. Rhodium/Yanphos-Catalyzed Asymmetric Interrupted Intramolecular Hydroaminomethylation of trans-1,2-Disubstituted Alkenes. *J. Am. Chem. Soc.* **138**, 9017-9020 (2016).

59. The result is different with that of our previous work on AHF initiated cascade reaction to form stable hemiacetal (ref. 47), only small amount of hemiacetal was detected on crude $^1$H NMR in this transformation, which was unstable on silicon gel column and transformed to aldehyde, giving aldehyde $2a$ in 94% isolated yield.
60. The target product 3w can be prepared under standard reaction conditions, but it was difficult to obtain pure 3w due to the low boiling point, thus only the data of 2w was provided.

61. Krall J, Jensen C H, Bavo F, Falk-Petersen C B, Haugaard A S, CVogensen S B, Tian Y, Nittegaard-Nielsen M, Sigurdardottir S B, Kehler J, Kongstad K T, Gloriam D E, Clausen R P, Harpsoe K, Wellendorph P, Frølund B. Molecular Hybridization of Potent and Selective γ-Hydroxybutyric Acid (GHB) Ligands: Design, Synthesis, Binding Studies, and Molecular Modeling of Novel 3-Hydroxycyclopent-1-enecarboxylic Acid (HOCPCA) and trans-γ-Hydroxycrotonic Acid (T-HCA) Analogs. *J. Med. Chem.* **60**, 9022-9039 (2017).