Silicon-oriented regio- and enantioselective rhodium-catalyzed hydroformylation

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Hydroformylation of 1,2-disubstituted alkenes usually occurs at the α position of the directing heteroatom such as oxygen atom and nitrogen atom. By contrast, to achieve hydroformylation on the β position of the heteroatom is a tough task. Herein, we report the asymmetric rhodium-catalyzed hydroformylation of 1,2-disubstituted alkenylsilanes with excellent regioselectivity at the β position (relative to the silicon heteroatom) and enantioselectivity. In a synthetic sense, we achieve the asymmetric hydroformylation on the β position of the oxygen atom indirectly by using the silicon group as a surrogate for the hydroxyl. Density functional theory (DFT) calculations are carried out to examine energetics of the whole reaction path for Rh/YanPhos-catalyzed asymmetric hydroformylation and understand its regioselectivity and enantioselectivity. Our computational study suggests that the silicon group can activate the substrate and is critical for the regioselectivity.

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Owing to the high atom economy, asymmetric hydroformylation (AHF) of alkenes provides an efficient way for the synthesis of enantioselectively pure aldehydes, which are versatile chiral intermediates for pharmaceuticals, agrochemicals, and other fine chemicals. In the past decades, intensive research efforts have been made in this area, and a range of chiral phosphorus ligand systems have been developed for AHF reactions, including BINAPHOS, bis(diazaphospholane) (BDP), Chiraphite, Ph-BPE, YanPhos, and other phosphorus ligands. Many simple terminal alkenes have been converted into chiral aldehydes with practical levels of regio- and enantioselectivity by AHF. However, for 1,2-disubstituted alkenes, the control of regioselectivity is a preeminent challenge because of the less steric difference between two substituent groups than in monosubstituted or 1,1-disubstituted alkenes. To address this issue, Tan et al. designed the scaffolding catalysis for allyl amines and alcohols, Reek et al. used the supramolecular catalysis in AHF of unactivated disubstituted olefins, and in terms of the substrate design, Landis et al. successfully achieved AHF of 1,2-disubstituted alkenes comprising (Z)-enol esters and enamides with Rh-BDP catalysts. Due to electron-withdrawing groups, high regioselectivities were given (up to >99:1) for AHF of (Z)-enol esters and enamides. The results suggest that the electronic and steric differentiation of the substituent groups is a key factor for the regioselectivity of this transformation. In these examples, CO was mainly incorporated at the α position of the oxygen atom or nitrogen atom. By contrast, to achieve the AHF on the β position of the heteroatom (O or N) is a tough task. Herein, we attempted to use the silicon group as a surrogate for the hydroxyl (via Fleming-Tamao oxidation) in a synthetic sense, and the β-aldehyde product is more favorable due to the steric hindrance of the silicon group. Based on these ideas, a series of 1,2-disubstituted alkenylsilanes were designed and Z-alkenes were chosen instead of E-alkenes because of higher regio- and enantioselectivities and faster rates. Organosilicon compounds are essential synthetic reagents and intermediates in modern organic synthesis, and the Si atom itself

![Fig. 1](image-url)
is a key element in many functional materials and bioactive molecules. Particularly, chiral β-aldehydesilanes are valuable intermediates, which can be readily converted to other versatile building blocks occurring in a variety of small molecule pharmaceuticals and natural products, such as drugs A (angiotensin-converting enzyme inhibitor), B (HIV protease inhibitor)38, fasiditri39, candoxatril40, venlafaxine41, tropicamide42, and natural products scopolamine43,44 and anisodamine45 (Fig. 1c).

**Results**

**Investigation of chiral ligands.** Our initial studies focused on the AHF of (Z)-trimethyl(styryl)silane (1a) to give the desired chiral aldehyde product 2a, with the expectations of achieving a highly regioselective and enantioselective transformation. To our delight, when (S,R)-(N-Bn)-YanPhos was employed, the reaction almost exclusively took place in the β position (the ratio of 2a/3a is >99) to produce 2a with 92% ee and 96% yield (Table 1, entry 1). As summarized in Table 1, an evaluation of ligands revealed (S,R)-(N-Bn)-YanPhos to be superior to all others tested (Table 1, entry 1 vs. entries 2–6). Rh catalysts based on other ligands, including XuPhos, (S,S)-Ph-BPE, (R,Cp)-DuanPhos, and (R)-QuinoXPh, exhibited high activity and excellent regioselectivity with low to good ee values, and almost no isomerization product was detected (Table 1, entries 2–5). (S)-BINAP, having axial chirality, was an unsatisfactory ligand for this reaction (Table 1, entry 6).

**Investigation of reaction conditions.** In order to achieve good regioselectivity and enantioselectivity and minimize the isomerization product 4a, which was produced via the olefin insertion to the Rh-H bond followed by β-hydride elimination, we sought to obtain optimal reaction conditions, as summarized in Table 2. We found that different solvents have an influence on the chemoselectivity, but a very small effect on the regioselectivity (Table 2, entries 1 and 3 –5). Interestingly, when tetrahydrofuran was used, the olefin isomerization product 4a was obtained as the main product, which may be due to the solvent coordination effect (Table 2, entry 2). Next, the influence of the L1/Rh ratio was investigated. Lowering of the L1/Rh ratio gave higher conversion, but the yield of the desired product 2a dropped significantly (Table 2, entry 2). When the L1/Rh ratio rose to 3, higher enantioselectivity (94% ee) with slightly lower yield (90% yield) was achieved (Table 2, entry 7). Under this ratio (L1/Rh = 3), the syngas pressure and reaction temperature were screened. The results indicated that lower syngas pressure and high temperature is beneficial to the conversion, which is consistent with the conclusion we have obtained for the YanPhos/Rh system (Table 2, entries 7–12). The complete conversion was achieved in 20 h under 10 bar of CO/H2 at 70 °C, affording near quantitative yield of the desired product 2a with 94% ee (Table 2, entry 8). Lower pressure (CO/H2 = 2/2 bar) was also tested, but no significant improvement was observed (Table 2, entry 9 vs. entry 8).

**The study of isomerization reaction.** To gain a deeper understanding of the relationship between syngas pressure and
isomerization, the effects of syngas (CO/H₂ = 1:1), H₂, and CO partial pressure on the isomerization were investigated systematically (Supplementary Table 1). Firstly, 4a was used as the substrate directly and very low conversion (only 1%) was detected when the reactions were carried out in 20 h under 10 bar of syngas (CO/H₂ = 1:1) at 70 °C (Supplementary Table 1, entry 1), which indicates that it is almost impossible to transform 4a under current catalytic system. We also stopped the reaction at about 50% conversion (2a was used as the substrate, CO/H₂ = 5:5 bar, 70 °C, 3.5 h), but only trace (<1%) 4a was detected (Supplementary Table 1, entry 2), which means that the isomerization is very slow at low pressure. As shown in Fig. 2a, the ratio of 4a shows a strong dependence on the total syngas pressure (CO/H₂ = 1:1). To independently measure the effect of H₂ partial pressure on the isomerization, one set of experiments used 5 bar CO pressure while varying H₂ pressure from 5 to 15 bar. As shown in Fig. 2b, the ratio of 4a was almost unchanged as the H₂ pressure varied. The independent measure of the effect of CO partial pressure was also carried out, the H₂ pressure was held at constant 5 bar, and the CO partial pressure was varied from 5 to 25 bar. As shown in Fig. 2c, raising the CO partial pressure could promote the isomerization, which is opposite to the results in previous papers 49. We attempt to explain the problem from the mechanism, and proposed a proper path of the isomerization (Fig. 2d). Because of the competition between CO and the PN part of YanPhos for the rhodium center, A could convert to B, which is critical for the isomerization. The coordination of CO to the rhodium species makes the Rh center of B electron deficient, which leads the CO on the equatorial position more weakly coordinated, while the CO on the axial position could not achieve the CO insertion. These properties of B may promote the β-hydride elimination to form 4a 50. With the CO partial pressure increasing, B could be formed more easily, which leads to more isomerization.

Substrate scope. With the optimized conditions in hand, we explored the substrate scope and generality of this asymmetric transformation (Fig. 3). First, in order to investigate the influence of substituents on the silicon atom, we changed trimethylsilyl (1a) to dimethyl(phenyl)silyl (1b) and benzylmethylysil (1c). We found that when 1b was employed as the substrate, the desired product 2b was obtained with excellent regioselectivity and enantioselectivity albeit with 80% yield. While, 2c was achieved in 96% yield with 97% ee and slightly lower regioselectivity (β/α = 97:3). Because of the simple preparation, trimethylsilyl was chosen as one substituent of the alkene, and a series of arylolenes were synthesized and investigated. Many functional groups, such as methyl (2d), methoxyl (2e), tertiary butyl (2f), phenyl (2g), trifluoromethyl (2j), and halides (2h and 2i), are compatible with this transformation. It was found that, with electron-rich aryl alklenes, aldehyde products are formed in lower yields than that with electron-neutral and electron-deficient aryl alklenes. On the other hand, the regioselectivity and enantioselectivity are not obviously affected by the electrical properties of the benzene ring. Moreover, substrates with meta- or ortho- substitution on the phenyl group were readily accommodated (2k–2m). The highly electron-deficient substrate 1n was also well tolerated. Furthermore, good yields, regioselectivities, and enantioselectivities were obtained with a range of substrates containing other aromatic fragments, including naphthalenes, furans, and thiophenes (2o–2q). Then, more challenging substrates containing alkyl substituents were tested; to our delight, 2r and 2s were obtained with
Fig. 3 Asymmetric hydroformylation of Z-alkenylsilanes. Reaction conditions: 1 (0.5 mmol), Rh(acac)(CO)$_2$ (0.5 mol%), (S,R)-(N-Bn)-YanPhos (1.5 mol%), CO (5 bar), H$_2$ (5 bar), toluene (2 ml), 70 °C, 20 h. Isolated yields. Product ratios were determined by $^{1}$H NMR analysis of the unpurified reaction mixture. Enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase after NaBH$_4$ reduction. a 1.0 mol% Rh(acac)(CO)$_2$ and 3.0 mol% (S,R)-(N-Bn)-YanPhos were used.

Mechanistic studies. On the basis of the previous computational and experimental results on other Rh-catalyzed hydroformylation, we also carried out DFT calculations (using (S,R)-(N-Bn)-YanPhos and 1a) to examine energetics of the whole reaction path for this Rh-catalyzed AHF and understand its regioselectivity and enantioselectivity to gain more insightful understanding (Figs. 5 and 6). As shown in Fig. 5, the alkene insertion step was computed to be the rate-determining step, which is in agreement with the previous computational studies and no observation of the H/D scrambling from the product (Fig. 7). In addition, as to the rate-determining step, TSI$_{\text{TMS-}^{1}R}$ was computed to be lower in free energy than TSI$_{\text{TMS-}^{1}R}$ by 3.1 kcal/mol in solution (i.e., calculated $\beta/\alpha > 99.1$, Fig. 6a and b), which is consistent with the experimental result. On the other hand, TSI$_{\text{TMS-}^{1}R}$ is computed to be higher in free energy than TSI$_{\text{TMS-}^{1}R}$.
1.0 mol% Rh(acac)(CO)$_2$ (5 bar) + CO (5 bar) + H$_2$ (5 bar) + alkyl

1.0 mol% Rh(acac)(CO)$_2$ + 3.0 mol% (S,R)-(N-Bn)-YanPhos (3.0 mol%), CO (5 bar), H$_2$ (5 bar), toluene (2 ml), 70 °C, 20 h

Fig. 4 Substrate effect. Reaction conditions: 1 (0.5 mmol), Rh(acac)(CO)$_2$ (1.0 mol%), (S,R)-(N-Bn)-YanPhos (3.0 mol%), CO (5 bar), H$_2$ (5 bar), toluene (2 ml), 70 °C, 20 h. Yields and product ratios were determined by $^1$H NMR analysis of the unpurified reaction mixture. Enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase after NaBH$_4$ reduction.

Fig. 5 Computation studies on the mechanism. The migratory insertion of Rh-H to alkene was computed to be the rate-determining step and determines the regioselectivity and enantioselectivity. TS, transition state.

Fig. 6 DFT calculations. Gibbs free energies of the Rh-H insertion step. a Gibbs free energies of T$_{\text{SITMS-s15}}$. b Gibbs free energies of T$_{\text{SITMS-s15}}$. c Gibbs free energies of T$_{\text{SITMS-s15}}$. d Gibbs free energies of T$_{\text{SITMS-s15}}$. 

Δ$G_{\text{calc}}$(kcal/mol)

Δ$G$ = 29.2 kcal/mol
Δ$G$ = 32.3 kcal/mol
Δ$G$ = 31.5 kcal/mol
Δ$G$ = 31.3 kcal/mol
Δ$G$ = 29.2 kcal/mol
Δ$G$ = 32.3 kcal/mol
Δ$G$ = 31.5 kcal/mol
Δ$G$ = 31.3 kcal/mol

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\[ \begin{align*}
\text{PhSi} & \quad + \quad \text{CO} \quad (5 \text{ bar}) \quad + \quad \text{D}_2 \quad (5 \text{ bar}) \quad \xrightarrow{1.0 \text{ mol}\% \text{ Rh(acac})(CO)_2} \\
\text{SiPh} & \quad + \quad \text{CO} \quad (5 \text{ bar}) \quad + \quad \text{H}_2 \quad (5 \text{ bar}) \quad \xrightarrow{0.1 \text{ mol}\% \text{ Rh(acac})(CO)_2} \\
\beta & \quad + \quad \alpha
\end{align*}\]

Fig. 7 Deuteration experiments. The D incorporation in the products are >95% according to \(^1\text{H} \text{NMR}\)

**Applications of the transformation.** To demonstrate the synthetic utility of the current methodology, the reaction was conducted with lower catalyst loading (S/C = 1000), affording the desired aldehyde 2a in 93% yield with 92% ee and excellent regioselectivity (Fig. 8a). Gram scale reaction of 1c could also proceed smoothly, and high yield, excellent regio- and enantioselectivity were remained (Fig. 8b). Furthermore, a creative synthetic route for chiral tropic acid which can be readily converted to tropicamide, hyoscyamine, scopolamine and anisodamine was demonstrated (Fig. 8c). As shown in Fig. 6d, when 1w was used as the substrate, this asymmetric transformation suffers from a higher barrier in the alkene insertion step, which qualitatively explains poor reactivity. Both the experimental results and computational results reveal that the silane group plays a critical role in this reaction, especially in the control of the regioselectivity and the activation of the substrate.

**Discussion**

In conclusion, we develop an efficient approach for synthesizing valuable chiral \(\beta\)-aldehydesilanes by catalytic AHF of \(Z\)-alkenylsilanes. Because of the hindered silicon groups, this transformation exhibits excellent regioselectivities (\(\beta/\alpha\) up to >99), and respectively, the corresponding \(\beta\)-aldehydesilanes are obtained with excellent enantioselectivities (up to 97% ee) under mild reaction conditions with low catalyst loading. By using the transformations of aldehyde groups and silicon groups, the products can be useful synthetic intermediates for bioactive molecules and natural products. Moreover, experiment results and DFT calculations indicate that the silicon group are primary factors of the regiocontrol and substrates’ reactivity in this asymmetric transformation.

**Methods**

**General procedure for the AHF of alkenylsilanes.** In a glovebox filled with nitrogen, to a 5 ml vial equipped with a magnetic bar was added ligand \(L_1\) (0.0075 mmol) and \(\text{Rh(acac})(CO)_2\) (0.0025 mmol in 0.5 mL solvent). After stirring for 10 min, substrate (0.5 mmol) and additional solvent were charged to bring the total volume of the reaction mixture to 2.0 mL. The vial was transferred into an autoclave and taken out of the glovebox. Carbon monoxide (5 bar) and hydrogen (5 bar) were charged in sequence. The reaction mixture was stirred at 70 °C (oil bath) for 20 h. The reaction was cooled and the pressure was carefully released in a well-ventilated hood. The conversion and \(\beta/\alpha\) ratio were determined by \(^1\text{H} \text{NMR}\) spectroscopy from the crude reaction mixture. Enantioemic excesses (ee) were determined by HPLC analysis using a chiral stationary phase after \(\text{NaBH}_4\) reduction.

**Data availability.** The authors declare that the data supporting the conclusions of this study are available within the article and its Supplementary Information file or from the corresponding author upon reasonable request.

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Author contributions

C.Y. and X.L. contributed equally to this work. C.Y. and X.L. contributed to the conception and design of the experiments. C.Y., X.L., Y.-S.Y., S.L., and B.W. performed the experiments and analyzed the data. X.T. carried out the deuterium labeling experiment. Y.Y. and L.W.C. carried out the computations. C.Y. and H.L. wrote the manuscript with feedback and guidance from X.Z. H.L. and X.Z. directed the project. All authors discussed the experimental results and commented on the manuscript.

Additional information

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