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RESEARCH ARTICLE

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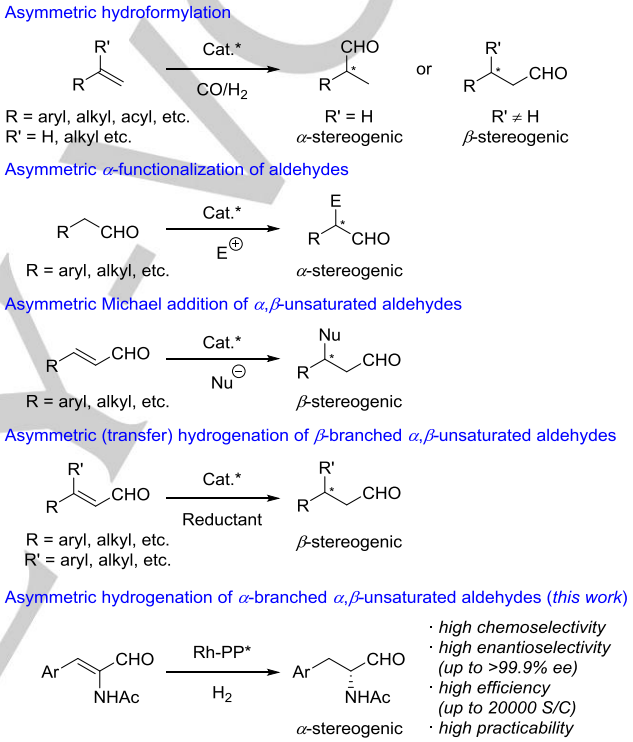
Chemo- and Enantioselective Hydrogenation of α-Formyl Enamides: An Efficient Access to Chiral α-Amido Aldehydes

Jian Zhang,[a] Jia Jia,[b] Xincheng Zeng,[a] Yuanhao Wang,[a] Zhenfeng Zhang,[a] Ilya D. Gridnev,[c] and Wanbin Zhang*[a,b]

Abstract: In order to effectively synthesize chiral *α*-amino aldehydes, which have a wide range of potential applications in organic synthesis and medicinal chemistry, a highly chemo- and enantioselective hydrogenation of *α*-formyl enamides has been developed, catalyzed by a rhodium complex of a P-stereogenic bisphosphine ligand. Under different hydrogen pressures, the chiral *α*-amido aldehydes and *β*-amido alcohols were obtained in high yields (97-99%) and with excellent chemo- and enantioselectivities (up to >99.9% ee). The hydrogenation can be carried out on a gram scale and under a high substrate/catalyst ratio (up to 20000 S/C), and the hydrogenated products were further converted to several important chiral products. Computations of the catalytic cycle gave a clear description for the *R*/*S*-pathways, provided a reasonable explanation for enantioselectivity, and revealed several other specific features.

Introduction

In the field of synthetic chemistry, aldehydes play a critical role not only due to their wide applications as bioactive compounds, but also because of their ability to be derivatized to various useful functional groups, such as alcohols, carboxylic acids, esters, and amines. Similarly, chiral aldehydes are very common structural units and key intermediates in natural products, pharmaceuticals, flavors, etc.[1] These important and versatile uses have made the synthesis of chiral aldehydes attractive (Scheme 1). The main developing methodologies for the enantioselective synthesis of such compounds include the asymmetric hydroformylation of alkenes,[2] *α*-functionalization of aldehydes,[3] Michael addition of *α*,*β*-unsaturated aldehydes,[4] and transfer hydrogenation of *α*,*β*-unsaturated aldehydes.[5] However, these methods do not satisfy the requirements for industrial use because of several shortcomings, such as low efficiency, high cost, poor atom economy, and being damaging to the environment. Therefore, an alternative and innovative approach is still highly desired.



Scheme 1. Asymmetric synthesis of chiral aldehydes.

Asymmetric hydrogenation (AH) is one of the most practical methodologies due to its high efficiency and environmental friendliness.[6] Until now, the AHs of *α*,*β*-unsaturated carboxylic acids, esters, amides, and even ketones have been developed with considerable success.[7] However, the AH of *α*,*β*-unsaturated aldehydes has not been widely reported. Only a handful of methodologies have been reported for the AH of *β*-branched *α*,*β*-unsaturated aldehydes with unsatisfactory enantioselectivity and efficiency.[8] Furthermore, the AH of *α*-branched *α*,*β*-unsaturated aldehydes is yet to be divulged. The difficulty for such reactions arises due to the problem of obtaining both high chemo- and enantioselectivity in a molecule containing both vinyl and formyl groups. Another significant problem concerns the racemization of *α*-stereogenic aldehydes in an acidic or basic medium. Over our research endeavors related to AH reactions,[9] we have successfully achieved chemo- and enantioselectivity by utilizing conjugated substrates bearing an amido directing group and an electron-rich bisphosphine-Rh catalytic system in a neutral medium.[9f,g,i,j]

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Inspired by these results, we envisaged that *α*-stereogenic aldehydes could be prepared using similar strategies (Scheme 1). Herein, we disclose the first example of a chemoselective AH of *α*-amido-substituted *α*,*β*-unsaturated aldehydes for the synthesis of chiral *α*-amido and *α*-amino aldehydes. These are important structural units and key intermediates for the synthesis of bioactive compounds, natural products and pharmaceuticals (Figure 1).[10]

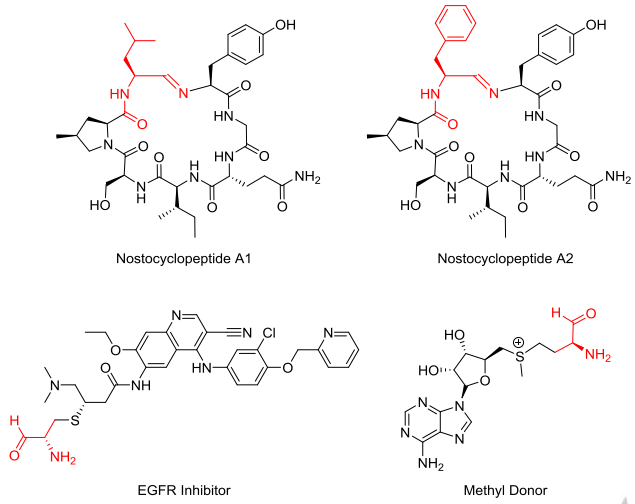
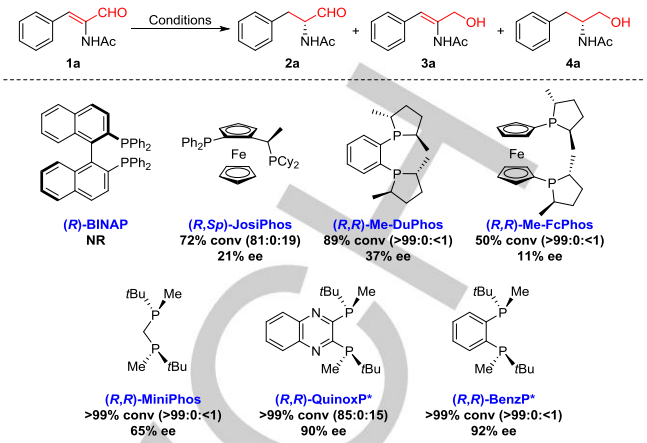


Figure 1. The importance of chiral *α*-amido and *α*-amino aldehydes.

Results and Discussion

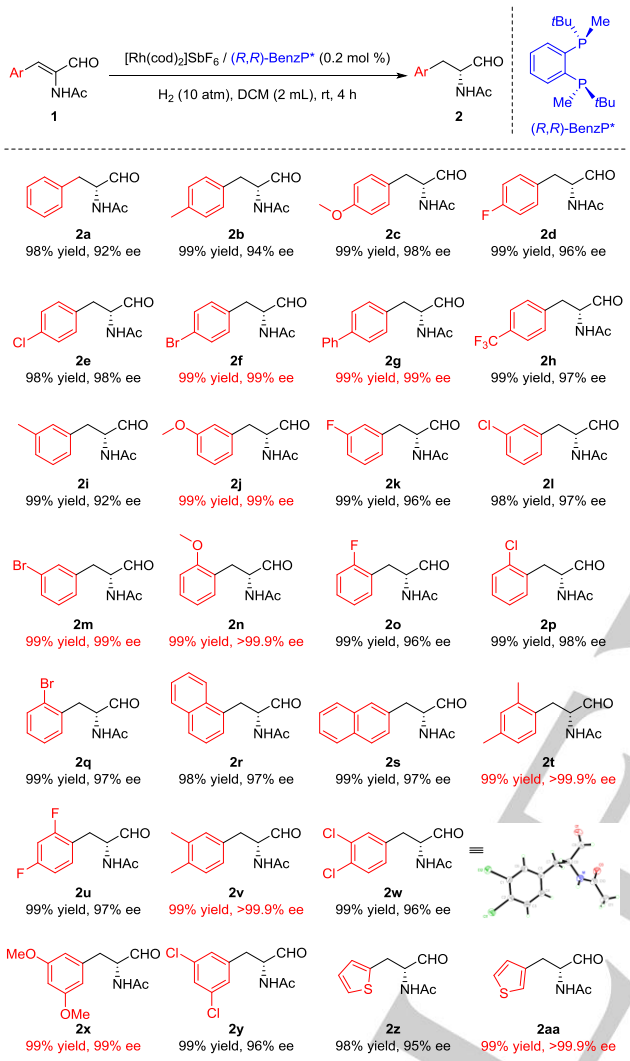
Initially, the model substrate **1a** was tested in the Rh-catalyzed asymmetric hydrogenation (Scheme 2). (*R*)-BINAP showed almost no reactivity. The desired product **2a** could be obtained in good conversion, good chemoselectivity (**2a**:**3a**:**4a** = 81:0:19) but poor enantioselectivity by using (*R*,*Sp*)-JosiPhos. The electron-rich bisphosphine ligands (*R*,*R*)-Me-DuPhos and (*R*,*R*)-Me-FcPhos afforded excellent chemoselectivities (**2a**:**3a**:**4a** = >99:0:<1) but still with unsatisfactory conversions and enantioselectivities. The P-stereogenic ligands (*R*,*R*)-MiniPhos, (*R*,*R*)-QuinoxP* and (*R*,*R*)-BenzP* promoted the hydrogenation with complete conversions. The (*R*,*R*)-MiniPhos showed moderate enantioselectivity of 65% ee, while (*R*,*R*)-QuinoxP* gave comparatively lower chemoselectivity (**2a**:**3a**:**4a** = 85:0:15). To our delight, the rhodium complex of (*R*,*R*)-BenzP*[11] showed the most promising stereocontrol, giving the desired product with both excellent chemoselectivity (**2a**:**3a**:**4a** = >99:0:<1) and high enantioselectivity of 92% ee. Subsequently, other reaction conditions were optimized (see Table S1 in Supporting Information for details). Most of the solvents gave high conversions and chemoselectivities, but no further increasing in enantioselectivity was observed. The hydrogenation was completed at 10 atm hydrogen pressure with a maintained enantioselectivity. The over-reduced product **4a** was obtained exclusively when increasing hydrogen pressure and prolonging reaction time. Under these reaction conditions, the by-product **3a** was not observed at all.



Scheme 2. Ligand screening. Conditions: **1a** (1.0 mmol), ligand (0.0021 mmol), $[Rh(cod)_2]SbF_6$ (0.002 mmol), H_2 (30 atm), DCM (2 mL), rt, 4 h. The conversions were calculated from ^{1}H-NMR spectra. The proportions of **2a**:**3a**:**4a** were calculated from ^{1}H-NMR spectra. The ee values of **2a** were determined by HPLC using chiral columns after the isolated aldehyde **2a** was reduced to the corresponding alcohol **4a** by $NaBH_4$.

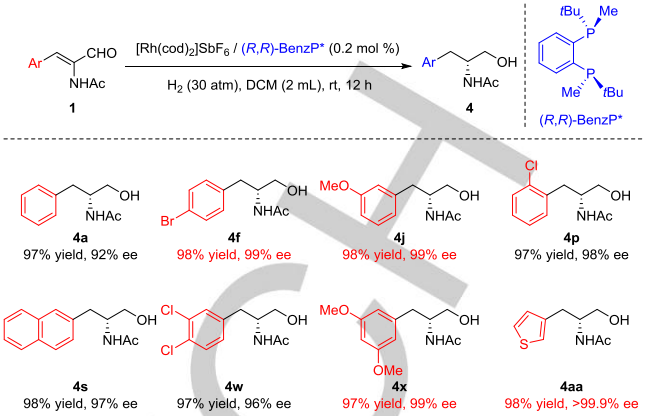
With the optimized reaction conditions in hand (Table 1, entry 19), we investigated the substrate scope for the synthesis of *α*-amido aldehydes (Scheme 3). All the reduced products, regardless of the electronic properties and the steric hindrance of the substituents, were obtained in excellent yields, chemoselectivities, and enantioselectivities. For a substrate bearing an electron-donating methyl substituent at the 4-position, the desired product **2b** was obtained in 94% ee. Increasing the electron-donating ability of the substitutents by changing the methyl group to a methoxy group showed a great effect on enantioselectivity. The product **2c** was obtained with higher enantioselectivity (98% ee). 4-Halogen-substituted compounds showed an increasing tendency in enantioselectivity with the corresponding products **2d**-**2f** being obtained with 96%, 98%, and 99% ee values, respectively. The product **2g** bearing a 4-phenyl group was produced with 99% ee, whereas the 4-CF_3-substituted **2h** was obtained with a slightly lower enantioselectivity of 97% ee. A similar trend was observed for the products **2i**-**2m**, possessing 3-substituents, with that of the 4-substituted **2b**-**2f**. The products **2n**-**2q** bearing 2-substituents also gave excellent enantioselectivities, especially 2-methoxy-substituted **2n** which was obtained with >99.9% ee. Disubstituted substrates bearing a 1-naphthyl or 2-naphthyl group gave the corresponding products **2r** and **2s** with comparable enantioselectivities. Other disubstituted substrates bearing electron-donating groups gave their desired products with better ee values than those bearing electron-withdrawing groups (**2t**-**2y**). More specifically, the product **2t,** with 2,4-dimethyl substituents, was obtained with much better ee than **2u** which possesses 2,4-difluoro substituents. A substrate bearing 3,4-dimethyl substituents gave the product **2v** with better ee than a substrate bearing 3,4-dichloro substituents**.** The product **2x** bearing 3,5-dimethoxy substituents was obtained with better results than **2y** which possesses 3,5-dichloro substituents. Furthermore, substrates processing heteroaryl groups, such as 2-thienyl and 3-thienyl, were also amenable to this catalytic

system, affording **2z** and **2aa** quantitatively with 95% and >99.9% ee values, respectively. The absolute configuration of the chiral α-amido aldehydes were considered to be the same as **2w** whose configuration was assigned to be *R* by X-ray single-crystal analysis.[12]



Scheme 3. Substrate scope to synthesize *α*-amido aldehydes. [a] Conditions: **1** (1.0 mmol), (*R*,*R*)-BenzP* (0.0021 mmol), $[Rh(cod)_2]SbF_6$ (0.002 mmol), H_2 (10 atm), DCM (2 mL), rt, 4 h. Isolated yields were recorded. The ee values of **2** were determined by HPLC using chiral columns after the aldehydes were reduced to the corresponding alcohols by $NaBH_4$.

β-Amido alcohols can also be obtained by extending the reaction time under a relatively high hydrogen pressure (Scheme 4). We chose representative substrates that have different electronic and steric properties, and possess multiple substituted groups. All the *β*-amido alcohols were obtained in excellent yields and enantioselectivities. Among them, the products **4f**, **4j**, or **4x** bearing 4-Br, 3-OMe, or 3,5-diOMe groups, respectively, were obtained in 99% ee, and the product **4aa** processing a thienyl substituent was produced quantitatively with >99.9% ee.



Scheme 4. Substrate scope to synthesize *β*-amido alcohols. [a] Conditions: **1** (1.0 mmol), (*R*,*R*)-BenzP* (0.0021 mmol), $[Rh(cod)_2]SbF_6$ (0.002 mmol), H_2 (30 atm), DCM (2 mL), rt, 12 h. Isolated yields were recorded. The ee values of **4** were determined by HPLC using chiral columns.

To demonstrate the potential utility of the protocol for the synthesis of chiral *α*-amido aldehydes, the hydrogenation was carried out on a gram scale and under a high substrate/catalyst ratio; the hydrogenated products were further converted to several important chiral products (Scheme 5). The reaction was conducted in DCM with 10 atm H_2 at room temperature catalyzed by (*R*,*R*)-BenzP*/$[Rh(cod)_2]SbF_6$ under 20000 S/C, affording the desired products **2a**, **2c** and **2e** in high yields and excellent enantioselectivities. Compound **2a** was subsequently used to synthesize the chiral *α*-alkynyl amine **5** employing the Ohira-Bestmann reagent.[13] The hydrogenated product **2q** was deacetylated under an acidic environment and ring closed to generate the chiral indoline-2-carbaldehyde **7**. Alternatively, under the conditions of a Pinnick oxidation, the chiral indoline-2-carbaldehyde was transformed to the chiral indoline-2-carboxylic acid **8** which is a key intermediate in drug synthesis.[14] Furthermore, using a Witting reagent, the aldehyde **9** can be easily converted to chiral olefin **10**, which can be transformed to a novel class of mixed D_2/D_4 receptor antagonists.[15] The chiral nitrile **11**, which can be utlized for the synthesis of ester bioisosteres with cardioprotective efficacies,[16] was accessed by sequential treatment of chiral aldehyde **9** with hydroxylamine hydrochloride and CDI (1,1'-carbonyldiimidazole). The amido alcohol **4a**, obtained directly under 30 atm H_2 pressure and after a 12 h reaction time, was smoothly hydrolyzed to the coorresponding chiral phenylglycinol **12**, followed by condensation and substitution to obtain a bisoxazoline ligand **14** which has been widely applied in many asymmetric catalyzed reactions.[17] Compound **1u** was reduced to the corrsponding alcohol directly under 30 atm. A subsequent ring closing reaction under alkaline conditions gave the chiral product **16**, an important chromane skeleton. The absolute configuration of **16** was assigned to be *R* by X-ray single-crystal analysis.[12]

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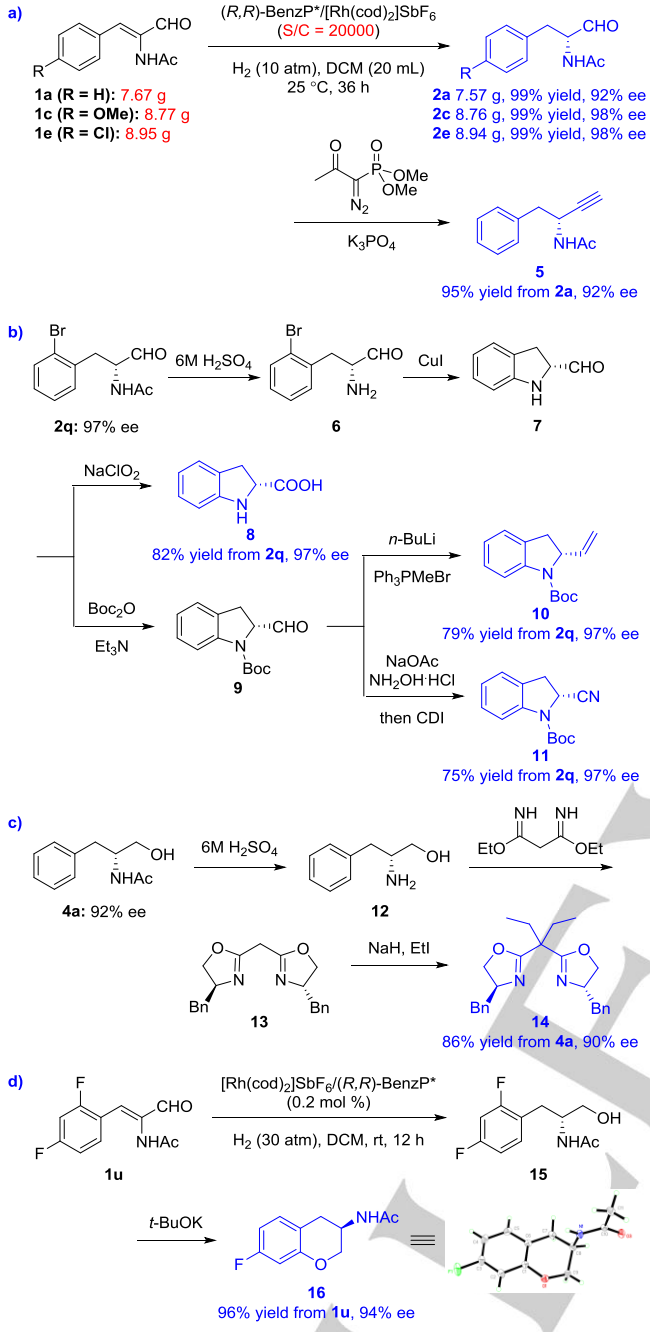


Scheme 5. Scale-up and applications.

Computations of the catalytic cycle gave a clear description for the *R*/*S*-pathways, provided a reasonable explanation for enantioselectivity, and revealed several other specific features (Scheme 6 and Scheme S1 in Supporting Information). BenzP*-Rh **17** can form three chelate catalyst-substrate complexes with similar stabilities. Unlike all previously studied cases,[10b,18,19] in the resting state, the *si-gauche*-coordinated catalyst-substrate complex **25** was computed to be more stable than normally coordinated *re*- and *si*-coordinated complexes by 0.9 and 2.5 kcal/mol respectively (see SI for details). Formation of a similar *re-gauche*-coordinated complex is not possible, since it would require formation of the chelate cycle in the hindered quadrant. Instead, formation of a *semi*-coordinated complex **18** stabilized by weak intramolecular interactions is observed (Figure 2). Normal *re*- and *si*-coordinated complexes have stabilities similar to that of **25**, but the oxidative addition of hydrogen to these complexes is significantly less facile (see SI for details). The complex **18** was computed to be the most active in the hydrogen activation step yielding dihydride **20a** via **TS1**. The complex **25** is capable of producing a similar dihydride **20b** by oxidative addition via **TS6** and further dissociation of the double bond via **TS7**. Via **TS8**, a reverse transformation of **20b** yields **26** instead of the expected non-chelating molecular hydrogen complex. Although the dihydride **27** is capable of a feasible migratory insertion, the resulting monohydride intermediate has the hydride and carbon ligands in a *trans*-position, thus excluding the possibility of reductive elimination, whereas the possible rearrangement routes are also high in energy (see SI for details).

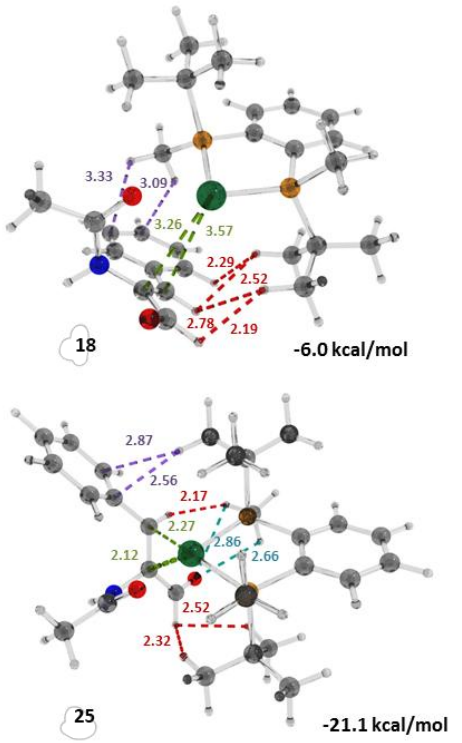
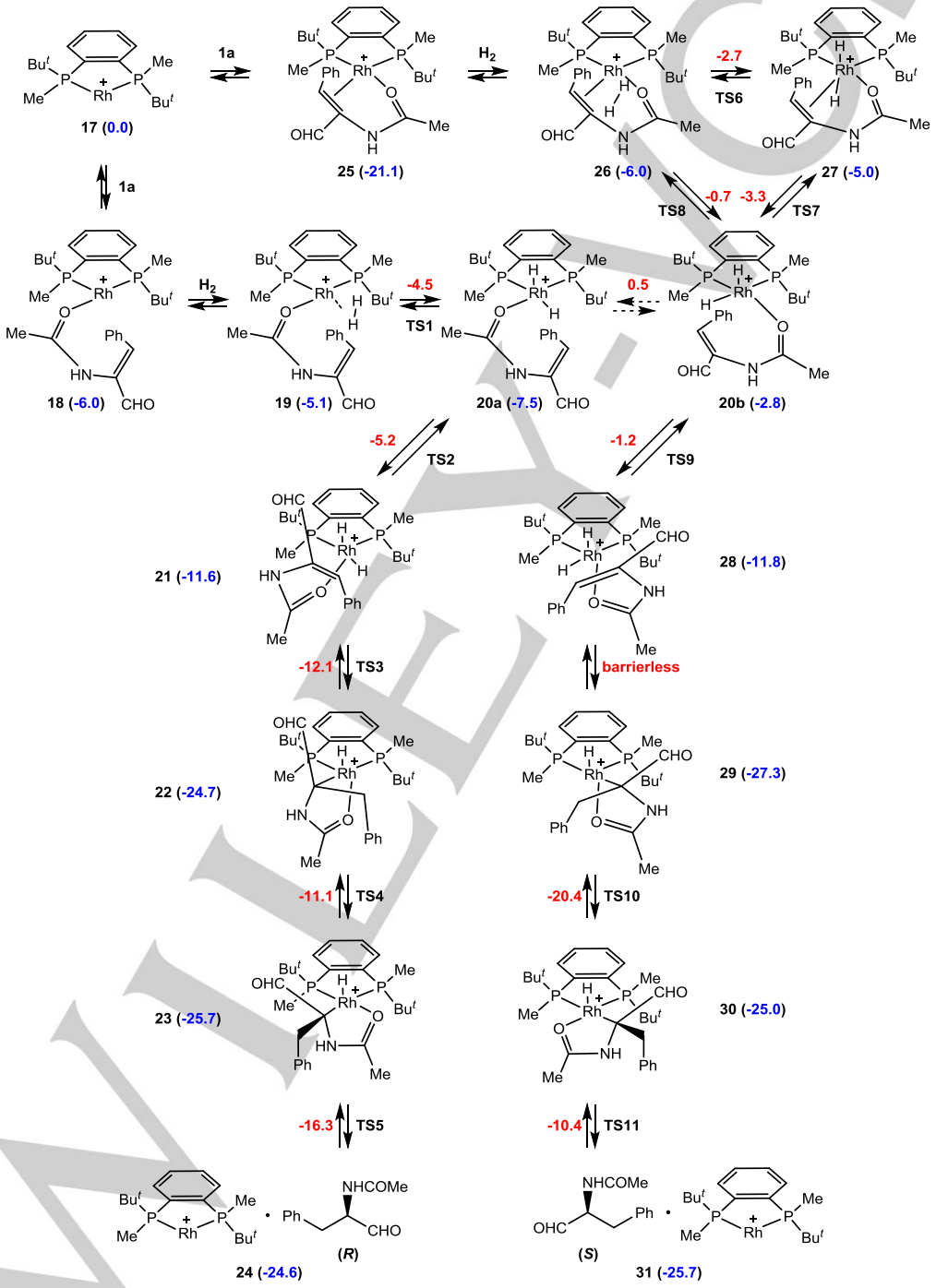


Figure 2. Optimized structures of the intermediates most active in activation of hydrogen. Up: non-chelating catalyst-substrate complex **18**; bottom: *si-gauche* coordinated catalyst-substrate complex **25**. Note the importance of the CHO group for stabilization of either **18** or **25** via weak intramolecular interactions: CH···HC (red), CH···π (violet), and CH···O (blue).

The double bond of the substrate is not coordinated in either **20a** or **20b**, therefore the absolute configuration of the hydrogenation product is determined by the preferential mode of the double bond coordination. Careful scanning of this process afforded the transition states **TS2** and **TS9** differing in free energy by 4.0

kcal/mol, thus demonstrating a strong bias towards formation of the *R*-product due to the preferential formation of the chelate cycle in a non-hindered quadrant (see SI for the routes via *β*-coordination that are characterized by significantly higher barries for the migratory insertion). However, realization of this scenario involves facile interconversion of **20a** and **20b**, whereas computations show that this interconversion requires overcoming a barrier approximately 5 kcal/mol higher than that required for the formation of the *R*-product (see SI for details). Hence, we conclude that in this particular case, the stereoselection may be constrained by the lack of convergence between the two alternative pathways for hydrogen activation. In that case the enantioselectivity is determined by a difference of 1.8 kcal/mol between the free energies of **TS1** and **TS6** that is in good agreement with the experimental value of 92% ee.



Scheme 6. Computed catalytic cycle. Blue numbers correspond to the energies of the intermediates, while the red numbers are the energies of the transition states.

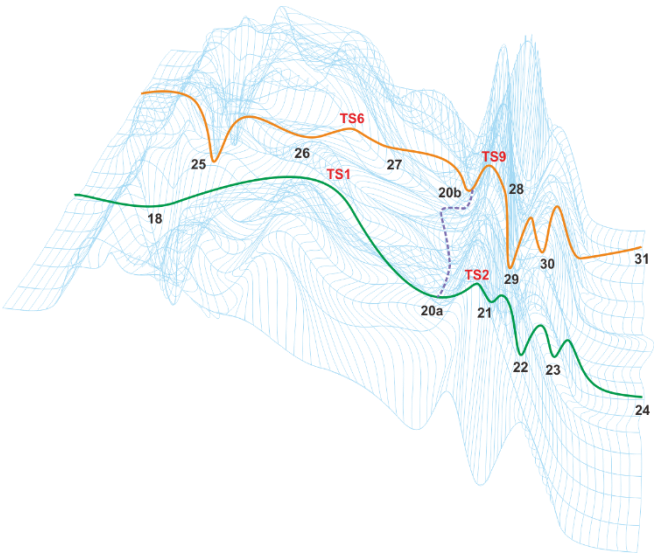


Figure 3. Schematic profile of potential energy for the catalytic cycle of hydrogenation of **1a** catalyzed by **17**.

One must realize that in view of the sophisticated catalytic cycle, reversible until the very last stage (Figure 3), accurate quantitative predictions of the optical yields are problematic. The highly uniform outcomes of the sense and order of enantioselection in the Rh-catalyzed asymmetric hydrogenation must be due to the competition in the process of the chelate cycle formation immediately prior to the almost barrierless migratory insertion step.[18] With regards to the hydrogen activation steps, **TS1** and **TS6,** belonging to different pathways, are competing, resulting in different rates of formation for **20a** and **20b,** respectively. Therefore, if interconversion of **20a** and **20b** is relatively slow, the optical yield of the product will be determined by the difference in the free energies of **TS1** and **TS6**. A relatively facile interconversion of **20a** and **20b**[19a,p] or significantly higher stability of **TS1** compared to that of **TS6**[11b] would change the enantioselective stage to the double bond coordination in **20a** and **20b**, and the difference in free energies of **TS2** and **TS9** would determine the optical yield of the hydrogenation product.[18b,c] The path that requires least energy for the interconversion between **20a** and **20b** computed for this catalytic cycle requires overcoming a relative free energy barrier of 0.5 kcal/mol (formation of a non-chelating molecular hydrogen complex from **20b**). This is higher in energy than **TS9**, hence **20b** is capable of producing some amount of the *S*-product. It is clear that in such a sophisticated system with various converging pathways and high level of reversibility, the relative rates of formation of opposite enantiomers depend on a larger number of kinetic and thermodynamic parameters. However, the relative stabilities of **TS1** and **TS6** are still very important, and if **TS1** is much more stable than **TS6**, the more reliable mechanism of stereodiscrimination via the difference in stabilities of **TS2** and **TS9**[18b,c,19p] remains undisturbed. Thus, the computational results provide a convincing account for the cases of perfect enantioselection observed in this study. On the other hand, the multitude of equilibria comprising the catalytic cycle is certainly quite susceptible to the changes in the structure of the substrate and reaction conditions, therefore the examples with slightly lower selectivities are not surprising.

Conclusion

In summary, we have developed a highly efficient route for the synthesis of chiral α-amido aldehydes. The desired products were obtained with high yields and with excellent chemo- and enantioselectivities (up to 99% yield and >99.9% ee). High catalytic activities were also observed (up to 20000 S/C). The reaction could be conducted on a gram scale and was further applied to the synthesis of several useful chiral compounds. DFT computations for the catalytic cycle gave a clear description for the *R*/*S*-pathways, provided a reasonable explanation for enantioselectivity, and revealed several other specific features.

Experimental Section

(*R,R*)-BenzP* ligand (0.59 mg, 0.0021 mmol) and $[Rh(cod)_2]SbF_6$ (1.11 mg, 0.002 mmol) were dissolved in anhydrous and degassed DCM (2 mL) under nitrogen. The mixture was allowed to stir for 30 min at room temperature. The substrate (1.0 mmol) was placed in a 5.0 mL tube equipped with a magnetic stirrer bar. This tube was put into an autoclave. The pre-prepared solution of catalyst was added under a nitrogen atmosphere. After purging with hydrogen three times, the hydrogen pressure was finally pressurized to 10 atm. The reaction mixture was vigorously stirred at room temperature for 4 h. The conversion of the product was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture and the yield was calculated after isolation by flash chromatography. The ee value was determined by chiral HPLC after transforming the formyl group to the corresponding hydroxymethyl group by $NaBH_4$.

Acknowledgements

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Keywords: hydrogenation • enantioselective • chemoselective • α-formyl enamides • α-amido aldehydes

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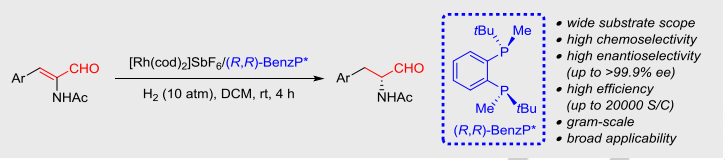

A highly chemo- and enantioselective hydrogenation of α-formyl enamides has been developed for the synthesis of chiral α-amido aldehydes in high yields (98-99%), excellent chemo- and enantioselectivities (up to >99.9% ee), and with high substrate/catalyst ratios (up to 20000 S/C).

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Chemo- and Enantioselective Hydrogenation of α-Formyl Enamides: An Efficient Access to Chiral α-Amido Aldehydes