Asymmetric Hydrogenation of γ-Branched Allylamines for the Efficient Synthesis of γ-Chirogenic Amines

Jian Zhang[1], Yuanhao Wang[1], Fengfan Zhou[1], Zhenfeng Zhang[1], Ilya Gridnev[2], and Wanbin Zhang[1]

[1]Shanghai Jiao Tong University
[2]Tohoku University

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Abstract

The efficient construction of γ-chirogenic amines has been realized via asymmetric hydrogenation of γ-branched N-phthaloyl allylamines by using a bisphosphine-Rh catalyst bearing a large bite angle. The desired products possessing different types of γ-substituents were obtained in quantitative yields and with excellent enantioselectivities (up to >99.9% ee). This protocol provided a practical method for the preparation of γ-chirogenic amine derivatives such as the famous antidepressant drug Fluoxetine (up to 50000 S/C). The mechanism calculation shows a weak interaction-promoted activation mode which is completely different from the traditional coordination-promoted activation mode in the Rh-catalyzed hydrogenation.

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Abstract: The efficient construction of γ-chirogenic amines has been realized via asymmetric hydrogenation ofγ-branched N-phthaloyl allylamines by using a bisphosphine-Rh catalyst bearing a large bite angle. The desired products possessing different types of γ-substituents were obtained in quantitative yields and with excellent enantioselectivities (up to >99.9% ee). This protocol provided a practical method for the preparation of γ-chirogenic amine derivatives such as the famous antidepressant drug Fluoxetine (up to 50000 S/C). The mechanism calculation shows a weak interaction-promoted activation mode which is completely different from the traditional coordination-promoted activation mode in the Rh-catalyzed hydrogenation.

Introduction

As versatile building blocks and synthetic intermediates, chiral amines play important roles in the construction of numerous valuable molecules. According to statistics, more than 40% of the top 200 listed small molecule drugs contain at least one chiral amine subunit in their structures. Therefore, the development of general and efficient methods to prepare chiral amines has been a major focus in both academia and industry.[1] In the process of pursuing this goal, catalytic asymmetric hydrogenation (AH) has gradually emerged as the most industrially feasible option due to its high efficiency, cost competitiveness and environmental friendliness.[2,3] Until now, hundreds of chiral transition metal catalysts have been developed and successfully applied in the asymmetric hydrogenation of thousands of structurally different$N$-containing substrates. The most representative research is the enantioselective synthesis of α-chirogenic amines by the catalytic asymmetric hydrogenation of enamines and imines (Scheme 1A), which was awarded the Nobel Prize in Chemistry of 2001 and has been used in several impressive industrial productions.[3]By contrast, the number of studies on the hydrogenative synthesis ofβ-chirogenic amines decreases significantly. One

route via the asymmetric hydrogenation of β -branched allylic amines is difficult due to the relatively low stability of the macrocyclic chelating intermediate.[4] Another route via the asymmetric hydrogenation of β -branched enamines is also difficult due to a relatively poor stereocontrol for the distinct substituted environment (Scheme 1B).[5] Therefore, it can be envisaged that the construction of γ -chirogenic amines via the asymmetric hydrogenation of γ -branched allylamines, which contains either of the above-mentioned difficulties for remote control, is a greater challenge (Scheme 1C). Until now, there have been no universal solutions with regards to this topic,[6]in spite of γ -chirogenic amines being required for the synthesis of important pharmaceuticals such as the antidepressant drugs Atomoxetine, Fluoxetine and Duloxetine, and the anti-muscarinic drug Tolterodine (Figure 1).

Scheme 1. Asymmetric hydrogenation for the synthesis of chiral amines.

Figure 1. The importance of γ -chirogenic amines.

Results and Discussion

Continuing our efforts to develop efficient asymmetric hydrogenations of challenging substrates, we are conviced that the additional coordination of a directing group to the metal and attractions between the ligand and substrate play a crucial role for both high reactivity and stereoselectivity.[5,7] Typically, catalyzed by a bisphosphine-Rh complex bearing a large bite angle (SKP[8] or SDP[9]) and assisted by a directing group (amide or ester) present in substrates,β -branched enamides or enols have been hydrogenated to produceβ -chirogenic amines or alcohols in quantitative yields and with excellent enantioselectivities.[5,7f] Inspired by these results, we are wondering whether the challenging asymmetric hydrogenation of γ-branched allylamines bearing a remote directing group, which is considered to form a larger and more unstable coordinating ring, can be realized by adopting a similar strategy. The experimental studies in this work will provide an unprecedented protocol for the efficient synthesis of γ -chirogenic amines, while the computational results will give a reasonable explanation for the catalytic mechanism and stereocontrol.

Initially, the model substrate **(*E*)-1a** was tested in the Rh-catalyzed asymmetric hydrogenation (Table 1). (*R*)-BINAP (the P-Rh-P angle of its Rh^I-complex: 92°),[10] (*R*)-DTBM-SegPHOS, (*R* ,*R*)-Me-DuPhos (85°)[11] and (*R* ,*R*)-QuinoxP* (86°)[12] showed almost no reactivity. The desired product could be obtained in good conversion, but poor enantioselectivity by using (*R* ,*R*)-BenzP* (85°).[13](*R*)-PhanePhos, (*R* ,*R*)-Me-FcPhos (the P-Rh-P angle of an analogous Rh^I-complex: 99°)[14] and (*R* ,*Sp*)-JosiPhos (the P-Rh-P angle of an analogous Rh^I-complex: 95°)[15] promoted the hydrogenation with complete conversions, however unsatisfactory enantioselectivities were still observed. Similar to the trend observed for the asymmetric hydrogenation of β -branched enol esters and β -branched enamides,[5,7f] the ligands (*R*)-SDP and (*R*)-SKP, bearing a large bite angle in their Rh^I-complexes (97° according to the XRD of [Rh((*R*)-SKP)(cod)]SbF_6 shown in Table 1), showed high activities and enantioselectivities. To our delight, the rhodium complex of (*R*)-SKP showed the most promising results, giving the desired product with both excellent conversion and a high enantioselectivity of 91% ee. After the screening of different solvents (entries 1-8), the enantioselectivity could be further increased to 92% ee by using ethyl acetate (EtOAc, entry 2). When the hydrogenation is carried out at lower hydrogenation pressures, the reactivity is reduced (entry 9). The substrate **(*Z*)-1a** gives the corresponding product with a better enantioselectivity of 97% ee but with the opposite configuration (entry 10). The substrate**(*E*)-1a-Bz** in which the phthaloyl group is replaced by a benzoyl group shows low reactivity and enantioselectivity (entry 11). Under the optimized reaction conditions, the substrate**(*E*)-1a-H** without phthaloyl group shows no reactivity (entry 12). The δ -branched substrate **(*E*)-1α-δ** , which possesses a longer distance between phthaloyl and vinyl groups, also shows no reactivity (entry 13). These results reveal that the presence of the phthaloyl group at a suitable position is important for the hydrogenation.

Table 1. Condition optimization.

entry[a]
1

2
3
4
5
6
7
8
9[d]
10
11
12
13

[a] Conditions: **1a** (0.2 mmol), (*R*)-SKP (0.0021 mmol), [Rh(cod)$_2$]SbF$_6$ (0.002 mmol), H_2 (50 atm), DCM (2 mL), rt, 12 h

With the optimized reaction conditions in hand, we investigated the substrate scope of γ ,γ -aryl/alkyl-substituted$N$ -phthaloyl allylamines with the (Z)-configuration at first. All the hydrogenated products, regardless of the electronic properties of R^1 and the steric hindrance of R^2, were obtained in excellent yields and enantioselectivities (Scheme 2). The electron-donating 4-methyl- and 4-ethyl-substituted amides **2b** and **2c** were obtained in 98% ee, while 4-*tert* -butyl substituted product **2d** was obtained with an excellent enantioselectivity of >99.9% ee. For substrates bearing

Scheme 2. Substrate scope of (Z)-1. Conditions:**(*Z*)-1** (0.2 mmol), (R)-SKP (0.0021 mmol), [Rh(cod)$_2$]SbF$_6$ (0.002 mmol), H_2 (50 atm), EtOAc (2 mL), rt, 12 h. Isolated yields were recorded. The ee values of **2** were determined by HPLC using chiral columns.

an electron-withdrawing 4-halogen group, the corresponding products**2e** and **2f** were obtained in 99% and 98% ee, respectively. The substrates bearing phenyl and nitro groups gave complete conversions and perfect enantioselectivities (>99.9% ee for **2g** and **2i**), while another product **2h** , with a trifluoromethyl at the *para* -position, was obtained with 99% ee. When the electron-donating methyl group was substituted at the *meta* -position, the enantioselectivity was maintained at 98% (**2j**), whereas the presence of a methyl group at the *ortho* -position resulted in a reduced enantioselectivity of 92% (**2l**). The substrates with a fluoro group at the*meta* -position provided the products with an excellent enantioselectivity of 99% (**2k**). Disubstituted substrates bearing a 1-naphthyl group gave the corresponding product **2q**with good enantioselectivity. Other disubstituted substrates bearing electron-withdrawing groups gave their desired products with better ee values than those bearing electron-donating groups (**2m** -**2p**). Additionally, substrates bearing$n$ -butyl as an R^2 substituent, which were synthesized from n -butyl lithium, have also been tested. The use of n -butyl instead of a methyl group led to an increase in enantioselectivity compared with the model product (**2r** vs**2a**), while the enantioselectivities of other products bearing different substituents remained at 99% (**2s** -**2u** vs**2k** , **2n** , **2p**). Furthermore, substrates processing heteroaryl groups, such as 2-thienyl and 3-thienyl, were also amenable to this catalytic system, affording **2v** and **2w**quantitatively with 96% and 95% ee values, respectively. To our delight, an alkyl-substituted substrate also accommodate this catalytic system, providing **2x** with an excellent enantioselectivity of 98%. The absolute configurations of γ-chirogenic amines in Scheme 2 were considered to be the same as **2g** whose configuration was assigned to be R by XRD analysis.

Subsequently, we studied the asymmetric hydrogenation ofγ ,γ -aryl/alkyl-substituted N -phthaloyl allylamines with the (E)-configuration. All the reduced products, regardless of the electronic properties of R^1 and the steric hindrance of R^2, were obtained in excellent yields and good to excellent enantioselectivities (Scheme 3). The electron-donating 4-alkyl-substituted amides **2b'** and **2y'** were obtained with 90% ee, while the electron-withdrawing 4-halogen-substituted products **2e'** , **2z'** and **2f'** were obtained with ees of 92%. The 4-CF_3-substituted product **2h'**was synthesized with an enantioselectivity of 92%, while the 4-Ph-substituted amide **2g'** showed a better ee of 94%. The substrates with methyl and fluoro group at the

meta -position provided the products **2j'** and **2k'** with complete conversions and better enantioselectivities (91% and 93% ee, respectively) than those bearing corresponding *para* -substituents. In contrast to the allylamides with a (*Z*)-configuration, the (*E*)-substrates have better enantioselectivities when the substituents are at the *ortho* -position. More specifically, the 2-methyl substituted amide **2l'** was obtained with 97% ee, while the 2-halogen-substituted amides **2aa'** and **2ab'** were both obtained in 98% ee. Disubstituted substrates bearing 3,5-dimethylphenyl, 3,5-dichlorophenyl, 1,3-benzodioxol-5-yl or 2-naphthyl moieties gave enantioselectivities between 90-93% (**2o'** , **2ac'** , **2ad'** and **2ae'**), while 1-naphthyl-substituted product **2q'** was obtained with an excellent enantioselectivity of 97%. Additionally, substrates bearing different R^2 substituents have also been tested. The use of larger alkyl substituents led to an increase in enantioselectivity (**2af' -2ah'**). However, the application of a benzyl group gave the product **2ai'** with a relatively lower ee of 87%. A substrate bearing γ -2-naphthyl andγ -phenyl groups was also subjected to hydrogenation to give the desired product **2aj'** with 86% ee. Furthermore, substrate processing a heteroaryl group such as a 2-thienyl ring was also amenable to this catalytic system, affording **2v'** with 73% ee. To our delight, alkyl substituted substrate are also ammenable to this catalytic system, providing the desired product **2x'** with 92% ee. The absolute configuration of the chiral γ -branched amides in Scheme 3 were opposite to the corresponding products in Scheme 2 according to the HPLC charts.

Scheme 3. Substrate scope of (*E*)-1. Conditions:**(*E*)-1** (0.2 mmol), (*R*)-SKP (0.0021 mmol), $[Rh(cod)_2]SbF_6$ (0.002 mmol), H_2 (50 atm), EtOAc (2 mL), rt, 12 h. Isolated yields were recorded. The ee values of **2'** were determined by HPLC using chiral columns.

Organofluorine compounds possess unique physicochemical properties and are highly important in medicinal, agricultural and material chemistry. Approximately 30% of all agrochemicals and almost 20% of all pharmaceuticals contain fluorine. However, the asymmetric introduction of fluorine into organic molecules is challenging. Hence, the development of new, simple and efficient methods to access a diverse array of novel chiral fluorinated derivatives, has become a highly prioritized research area.[16] Transition metal-catalyzed asymmetric hydrogenation of alkenyl fluorides is one of the most promising methods.[17] The relatively strong electron withdrawing behaviour of the fluorine together with the easy-to-break C–F bond, making these types of alkene substrates difficult to be hydrogenated. With the above-mentioned limitations in mind, we set out to develop the first efficient asymmetric hydrogenation of γ -aryl-γ -fluoro-substituted *N* -phthaloyl allylamines for the highly efficient synthesis ofγ -aryl-γ -fluoro-substituted chiral amines.

Scheme 4. Substrate scope of γ -fluoro-substituted allylamides. Conditions: **3** (0.2 mmol), (*R*)-SKP (0.0021 mmol), $[Rh(cod)_2]SbF_6$ (0.002 mmol), H_2 (10 atm), EtOAc (2 mL), -10 °C, 12 h. Isolated yields were recorded. The ee values of **4** were determined by HPLC using chiral columns.

Applying our previously optimized conditions (50 atm H_2, rt) to substrate **3a** gave only 30% of the desired product **4a** with 96% ee together with 70% de-fluorinated by-product. In order to solve the problem of de-fluorination, we further optimized the conditions. To our delight, decreasing the hydrogen pressure and reaction temperature to 10 atm and -10 °C respectively, successfully afforded the desired product **4a** in 95% yield and with 96% ee, and reduced the amount of de-fluorinated by-product to 5%. With the adjusted reaction conditions in hand, we investigated the substrate scope ofγ -fluoro allylamides with the (*Z*)-configuration (Scheme 4). The substrates with electron-withdrawing groups on the phenyl rings were well tolerated and generated the desired products in high isolated yields and with excellent enantioselectivities. The 4-halogen-substituted products **4b** and **4c** were obtained in 99% ee. The 4-CF_3-substituted product **4d**also gave an excellent ee of 99%. The 3-halogen-substituted products**4e** and **4f** were obtained with slightly lower enantioselectivities of 95% and 98%. For substrates bearing a fluorine at the 2-position, the desired product **4g** was obtained with 96% ee. Disubstituted substrates bearing electron-withdrawing groups also gave their desired products with excellent ee values (**4h -4k**). More specifically, the product **4i**with 3,4-dichloro substituents was obtained with a perfect enantioselectivity of >99.9% ee. The product **4j**bearing 3,5-difluoro substituents and the product **4k** bearing 3,5-dichloro substituents both gave their products with 99% ee. The absolute configurations of the chiralγ -aryl-γ -fluoro-substituted amides were considered to be the same as **4i** whose configuration was assigned to be *S*by XRD analysis.

Scheme 5. Substrate scope of γ -aryloxy-substituted allylamides. Conditions: **5** (0.2 mmol), (R)-SKP (0.0021 mmol), $[Rh(cod)_2]SbF_6$ (0.002 mmol), H_2 (50 atm), EtOAc (2 mL), rt, 12 h. Isolated yields were recorded. The ee values of **6** were determined by HPLC using chiral columns.

γ -Aryl-γ -aryloxy-substituted chiral amines are widely present in natural products and chiral pharmaceuticals, making the asymmetric catalytic synthesis of such compounds very attractive. As far as we know, no asymmetric hydrogenation of γ -aryloxy-substituted allylamides has been studied, probably due to difficulties related to the low activities of ene ethers and the poor stereocontrol of the reaction.

Using the previously optimized reaction conditions, we investigated the substrate scope of γ -aryloxy-substituted allylamides with a (Z)-configuration (Scheme 5). All the reduced products, regardless of the electronic properties and the steric hindrance of R^1, were obtained in excellent yields and enantioselectivities. γ -Phenyloxy-γ -phenyl-substituted amide **6a** was obtained in 95% ee. For a substrate bearing an electron-donating methyl substituent at the 4-position of aryloxy, the desired product **6b** was obtained in 97% ee. 4-Halogen-substituted compounds showed an increasing tendency towards better enantioselectivity with the corresponding products**6c** -**6e** being obtained with 98%, 99% and >99.9% ee values, respectively. The product **6f**bearing a 4-phenyl group was produced with 99% ee, while the 4-CF_3-substituted product **6g** was obtained with 96% ee. A similar trend was observed for the products**6h** -**6k** possessing 3-substituents with that of the 4-substituted ones. The product **6l** bearing a 2-fluorine group was also produced with 98% ee. Disubstituted substrates bearing electron-withdrawing groups gave the desired products with better ee values than those bearing electron-donating groups (**6m** -**6p**). The absolute configurations of the chiralγ -aryloxy-γ -phenyl-substituted amides were considered to be the same as **6e** whose configuration was assigned to be$S$ by XRD analysis.

To demonstrate the potential utility of the protocol for the synthesis of γ -chirogenic amines, the hydrogenation was carried out on a gram scale and under a high substrate/catalyst (S/C) ratio, and the hydrogenated products were further converted to several important pharmaceutical compounds (Scheme 6). The hydrogenation catalyzed by (R)-SKP/$[Rh(cod)_2]SbF_6$ under 20000 S/C afforded the desired product **2a** and **4m** in high yields and excellent enantioselectivities. Compound **2a** was smoothly hydrazinolyzed to the corresponding γ -chirogenic amine**7** , which can be further derivatized to a bioactive amide**8** in high yield with no loss in enantioselectivity. The product**4m** was hydrazinolyzed, ring closed and salified to generate 1,2,3,4-tetrahydro-4-methylquinoline hydrochloride **11** with perfect ee. For another example, the hydrogenation of **5a** at 5000 S/C produced the γ -fluoro-substituted amide in 93% yield and with 96% ee. In particular, the hydrogenation of **5g** could also be conducted in EtOAc under 50 atm H_2 at room temperature catalyzed by (S)-SKP/$[Rh(cod)_2]SbF_6$ under 50000 S/C, affording the desired product **6g** in high yield and excellent enantioselectivitiy. After changing the N -substituent from phthaloyl to methyl, the antidepressant drug Fluoxetine was obtained in 83% yield from **5g** and with >99.9% ee.

To gain insight into the reaction meachanism, deuterium experiment using D_2 instead of H_2 was conducted fort he hydrogenation of substrate **(*E*)-1a** , resulting in an exclusive deuterium addition to the vinyl group and with no alkene isomerization occurring (Scheme 7).

Scheme 6. Scale-up and applications.

Scheme 7. Deuterium experiment.

Computational calculations were conducted in order to gain further insight into the catalytic mechanism and stereocontrol. Unlike many other bisphosphine-Rh-catalyzed asymmetric hydrogenations,**SKP-Rh** does not demonstrate any capacity to form stable catalyst-substrate complexes with either E - or$Z$ -substrates. The corresponding minima for **SKP-Rh-Sub**complexes can be located, but they are extremely unstable (more than 10 kcal/mol endergonic) and do not involve any coordination between the catalyst and the double bond of the substrate. On the other hand, the formation of molecular hydrogen complex**SKP-Rh-H_2** and further dihydride complex**SKP-Rh-HH** via **TS-OA** are strongly exergonic. Actually, it is also possible to hydrogenate the extremely unstable**SKP-Rh-Sub** complexes with essentially the same result. The resting state consists of **SKP-Rh-HH** and uncoordinated substrate. It should be noted that the dihydride Rh^{III}-

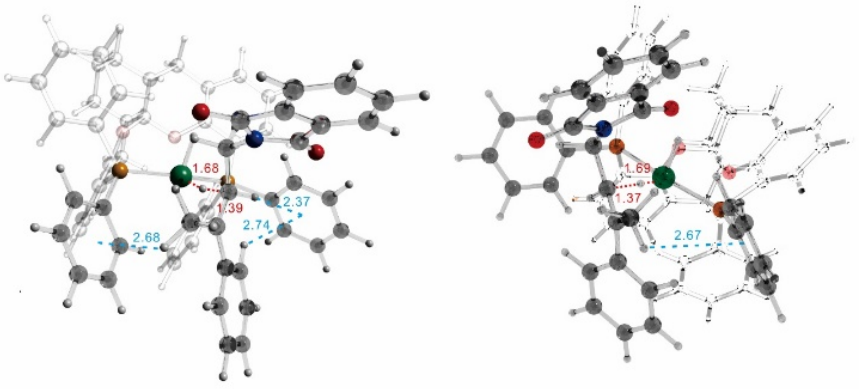
complex bears a P-Rh-P bite angle of 171.7° and does not contain a hydride *trans* to a phosphorus atom, that features in the way of its further reaction with the substrate (Figure 2). So far as we know, a similar form of coordination occurs only in pincer-metal complexes, and has not been reported in bidentate bisphosphine-metal complexes.[18]

Due to the configuration of the dihydride **SKP-Rh-HH** with extremely crowded space around Rh, the calculation also does not show coordination of the substrate's double bond to Rh in the**SKP-Rh-HH-Sub** complexes. The coordination is strongly endergonic and the complex is maintained by weak intramolecular interactions. This is completely different from the traditional coordination-promoted activation mode in the Rh-catalyzed hydrogenation.[12] Due to specific features of the substrate coordination, and flexibility of the conformations of the phenyl rings of the catalyst, there are numerous possibilities for substrate coordination, and hence for the following stages (see Supporting Information for details). The most possible pathways for the$E$ -substrate have been shown in Figure 3. Migratory insertion proceeds with reasonable activation barriers for both S- and$R$ -pathways, yielding the corresponding monohydrides**SKP-Rh-H-Int*S*** and **SKP-Rh-H-Int*R*** . Further reductive elimination gave the **SKP-Rh-Prod** complexes and dissociation of the substrate completes the catalytic cycle. According to the free energy profile, both migratory insertion and reductive elimination contribute to the enantioselectivity and a high barrier for reductive elimination may switch the stereoselection. The difference in Gibbs free energies between **TS-MI*S*** and**TS-MI*R*** is 7.0 kcal/mol in favor of the former.**TS-RE*R*** is more stable than **TS-RE*S*** by 3.8 kcal/mol. Hence, the whole catalytic cycle for the E -substrate is S-stereoselective with a free energy difference of 3.2 kcal/mol.

It also can be seen that the substrate selectively adopts a specific configuration to approach the Rh-hydride and thus forms a relatively stable transition state with more weak interactions between catalyst and substrate. Important weak intramolecular interactions in these transition states are shown in Figure 4. The red numbers show the position of the transferred hydride relative to the Rh and carbon atoms. Blue numbers show distances between the protons and centers of the phenyl rings characterizing the corresponding C-H$\ldots\pi$ interactions. There are other weak intramolecular interactions in both structures which roughly compensate each other. From **TS-MI*S*** and**TS-MI*R*** we can roughly estimate that the energy of two single C-H$\ldots\pi$ interactions is approximately 7.0 kcal/mol. From**TS-RE*S*** and **TS-RE*R*** we can roughly estimate that the free energy of a single C-H$\ldots\pi$ interaction is around 3.8 kcal/mol. The two results taken together give a [?]G [?] 4 kcal/mol for a C-H$\ldots\pi$ interaction of approximately 2.5 Å length. The authors realize that these evaluations are rough and approximate, but are strictly convinced that acquisition of such data is very important for quantification of weak interactions between the catalyst and substrate and are an ultimate goal of the mechanistic studies of enantioselective catalytic cycles.

Figure 2. Oxidative addition.

Figure 3. Migratory insertion and reductive elimination.



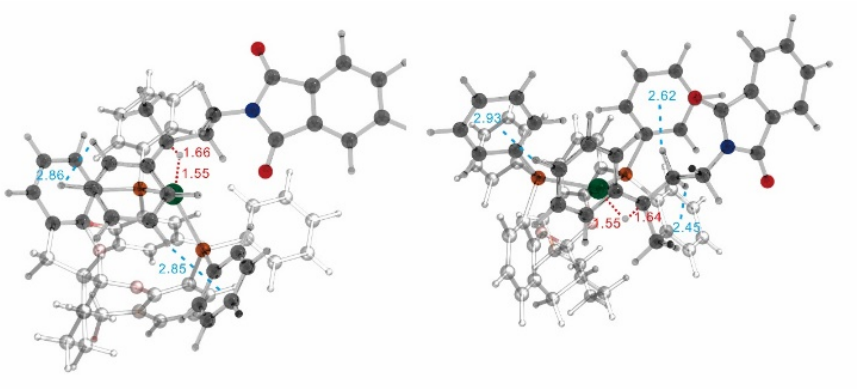


Figure 4. Migratory insertion and reductive elimination.

Conclusion

In summary, we have realized the enantioselective synthesis of γ-chirogenic amine derivatives via the asymmetric hydrogenation of γ-branched *N*-phthaloyl allylamines. A bisphosphine-Rh complex bearing a large bite angle was employed to provide the desired products with satisfactory yields and excellent enantioselectivities (up to >99% ee). This protocol was further applied to the preparation of some important pharmaceutical compounds, including the well-known antidepressant drug Fluoxetine (up to 50000 S/C). A nearly linear P-Rh^{III}-P coordination pattern and a weak interaction-promoted substrate-coordination activation mode, both of which are unusual in the bidentate bisphosphine-Rh-catalyzed hydrogenation, have been found according to the mechanism calculation.

Experimental Section

(*R*)-SKP 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 EtOAc (2 mL) under nitrogen. The mixture was allowed to stir for 30 min at room temperature. The substrate (0.2 mmol) was placed in a 5.0 mL tube equipped with a magnetic stirrer bar. This tube was placed in 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 50 bar. The reaction mixture was vigorously stirred at room temperature for 12 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.

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Keywords: asymmetric hydrogenation * bisphosphine ligand * SKP * chiral amines * allylamines

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