Rhodium-Catalyzed Asymmetric Transfer Hydrogenation of Heterocyclic Diaryl Ketones: Facile Access to Key Intermediate of Baloxavir

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Abstract

Transition metal-catalyzed asymmetric transfer hydrogenation has been proved to be a powerful approach for the synthesis of chiral alcohols. Herein, A highly efficient and enantioselective transfer hydrogenation of dibenzoheptaheterocyclic ketones catalyzed by an arene-tethered TsDPEN-based Rh(III) catalyst has been successfully developed, and a variety of dibenzoheptaheterocyclic ketones were reduced by a 1/1 mixture of formic acid and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) with high yields and enantioselectivities. With this method, the asymmetric reduction of 7,8-difluorodibenzo[b,e]thiepin-11(6H)-one has been realized, providing the key intermediate of baloxavir marboxil with >99% yield and >99% ee at a substrate/catalyst molar ratio of 1000.

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Rhodium-Catalyzed Asymmetric Transfer Hydrogenation of Heterocyclic Diaryl Ketones: Facile Access to Key Intermediate of Baloxavir

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Keywords

Asymmetric Transfer Hydrogenation | Baloxavir| Rhodium(III)|

Comprehensive Summary

Transition metal-catalyzed asymmetric transfer hydrogenation has been proved to be a powerful approach for the synthesis

Background and Originality Content

Baloxavir marboxil (trade name: Xofluza) was developed by Roche and Shionogi, and could be used to treat human influenza virus infections by inhibiting the synthesis of viral mRNA to block the proliferation of influenza virus.[1] As a third-generation anti-influenza virus chemical drug, baloxavir received its first global approval in Japan for the treatment of influenza A or B virus infections in February 2018,[2] subsequently baloxavir was approved by FDA in October. Baloxavir showed superior to Tamiflu in curative effect for influenza, for this indication, a single oral dose of baloxavir is recommended to be taken as soon as possible after onset of symptoms. Due to its excellent activity, the synthesis of baloxavir has attracted much attention from organic chemists. 7,8-difluorodibenzo[b,e]thiepin-11(6H)-one (**2a**) is an important intermediate of baloxavir, and baloxavir could be obtained from **2a** via a stereospecific Mitsunobu-type reaction (Figure 1).

Figure 1 Structures of baloxavir of its key synthetic intermediates

Scheme 1 Background and summary of this work.

In the original research,[3] $NaBH_4$was used for the reduction of compound **1a** to obtain racemic compound **2a** , the cumbersome separation and purification involved with this method greatly limits the synthetic efficiency, the development of efficient asymmetric synthesis of **2a** was highly desirable. So far, only the following reports were disclosed for the preparation of chiral compound **2a** . The first was carbonyl reductases (RtSCR9, EBSDR8, or PpYSDR) catalyzed reduction, which was patented by Zheng and coworkers in 2018,[4] and 99% ee was achieved (Scheme 1a). Although enzyme-catalyzed reduction had achieved good stereocontrol, the high dosage and price of enzymes limited the application in industrial production. In 2019, Zhang et al developed the asymmetric reduction of **1a** with (S)-2-methyl-oxazaborolidine as the chiral catalyst and BH_3 as the reductant (CBS reduction), the high catalyst loading and the low enantioselectivity (85%) greatly limited its synthetic application (Scheme 1b).[5] In 2021, a ruthenium-catalyzed asymmetric transfer hydrogenation of **1a** was patented by Zi and coworkers, they used Ru(p -cymene)TsDPEN as catalyst and azeotropic mixture of formic acid and triethylamine as the hydrogen donor, and 98% ee was achieved at 70 °C, further investigation and substrate scope of the reaction was not disclosed (Scheme 1c).[6] Our group has been devoted in asymmetric hydrogenation[7] and asymmetric transfer hydrogenation[8] for more than twenty years. In 2020, we disclosed a highly diastereoselective transfer hydrogenation of α-aminoalkyl α'-chloromethyl ketones in cooperation with Ratovelomanana-Vidal,[9] the tethered rhodium catalyst developed by Ratovelomanana-Vidal and Wills outperformed that of other catalysts.[10] Subsequently, the tethered rhodium has been applied in the dynamic kinetic asymmetric transfer hydrogenation of α-cyano ketones[11] and 3-hydroxy-4-substituted-maleimide derivatives[12]by our group and β-substituted α-diketones by Fang and coworkers.[13] As a continuation of investigation on asymmetric transfer hydrogenation, herein, we disclose a highly enantioselective asymmetric hydrogenation of heterocyclic diaryl ketones catalyzed by tethered rhodium catalyst (Scheme 1c).

Results and Discussion

Table 1 Optimization of the reaction conditions.

entry[a]	catalyst	solvent	hydrogen donor	yield (%)	ee (%)
1	**Cat1**	DCM	HCO_2H/Et_3N (5:2)	<5	—
2	**Cat2**	DCM	HCO_2H/Et_3N (5:2)	<5	—
3	**Cat3**	DCM	HCO_2H/Et_3N (5:2)	99	98
4	**Cat4**	DCM	HCO_2H/Et_3N (5:2)	40	98
5	**Cat5**	DCM	HCO_2H/Et_3N (5:2)	<5	—
6	**Cat6**	DCM	HCO_2H/Et_3N (5:2)	99	>99
7[b]	**Cat6**	THF	HCO_2H/Et_3N (5:2)	57	>99
8[b]	**Cat6**	DCM	HCO_2H/Et_3N (5:2)	35	99
9[b]	**Cat6**	toluene	HCO_2H/Et_3N (5:2)	56	99
10[b]	**Cat6**	MeCN	HCO_2H/Et_3N (5:2)	54	99
11[b]	**Cat6**	MeOH	HCO_2H/Et_3N (5:2)	12	99

entry[a]	catalyst	solvent	hydrogen donor	yield (%)	ee (%)
11[b]	**Cat6**	*i*PrOH	HCO_2H/Et_3N (5:2)	25	>99
12[b]	**Cat6**	THF	HCO_2H/Et_3N (3:2)	85	>99
13[b]	**Cat6**	THF	HCO_2H/Et_3N (1:1)	96	>99
14[b]	**Cat6**	THF	HCO_2H/DBU (1:1)	99	>99
15[b]	**Cat6**	THF	HCO_2H/DIPEA (1:1)	94	>99
16[b]	**Cat6**	THF	HCO_2Na	17	>99
17[b]	**Cat6**	THF	IPA	<5	—
18[c]	**Cat6**	THF	HCO_2H/DBU (1:1)	98	>99
19[d]	**Cat6**	THF	HCO_2H/DBU (1:1)	65	>99

[a] Unless otherwise specified, the reaction was conducted on 0.25 mmol scale at S/C = 200 for 6h.[b] S/C = 500. [c] S/C = 2000, 72 h. [d] S/C = 5000, 72 h.

We initiated our investigation with the optimization of the reaction conditions for the asymmetric transfer hydrogenation of **1a** , and the results were summarized in Table 1. At first, we screened various ruthenium, iridium and rhodium catalysts with azeotropic mixture of formic acid and triethylamine as hydrogen donor and DCM as solvent with a substrate/catalyst ratio of 200/1 at rt. <5% of **2a**was produced with Noyori and Ikariya's ruthenium catalyst**Cat1** [14] and iridium catalyst**Cat2** 15] (table 1, entry 1 and 2).[15] 99% yield and 98% ee were achieved with Noyori and Ikariya's rhodium catalyst**Cat3** .[15-16] The efficacy of Wills's tethered ruthenium catalyst **Cat4** [17] and Ikariya's oxo-tethered ruthenium catalyst**Cat5** [18] was also evaluated, 40% yield and 98% ee was observed with Wills's catalyst **Cat4** , whereas, only <5% yield was observed with Ikariya's catalyst**Cat5** . To our delight, the reaction with tethered rhodium catalyst **Cat6** [19] proceeded smoothly to provide the desired product **2a** with 99% yield and >99% ee, and **Cat6** was identified as the best catalyst for the current reaction. The effect of solvent on the current was also assessed with a substrate catalyst ratio of 500/1 and 99% ee were achieved for all the solvents screened (Table 1, entries 7-11), for aprotic solvents such as THF, DCM and toluene, 57%, 35% and 56% yield was obtained respectively. The yield was decreased to 12% and 15% with protic solvent MeOH and *i* PrOH respectively, and THF as identified as best solvent for the current reaction. Hydrogen donors were also found to have a great effect on the reactivity of the catalyst, when the ratio of formic and triethyl amine was changed from 5:2 to 3:2 and 1:1, the yield was improved to 85% and 96% respectively (Table, entries 12-13). When the triethyl amine was replaced with DBU the yield was further elevated to 99%, whereas the yield dropped to 94% with bulky DIPEA as base. Other hydrogen donors such as sodium formate and*i* PrOH were also tested, and <5 and 17% yield was achieved respectively (Table 1, entries 16-17). When the substrate-catalyst ratio was increased to 2000/1, 98% yield and >99% ee were obtained in 72 h, and the yield was dropped to 65% with a substrate catalyst ratio of 5000/1 (Table 1, entries 18-19).

With the optimal reaction conditions in hand, the substrate scope of this asymmetric transfer hydrogenation was investigated, and the results were depicted in Scheme 2. For a series of dibenzoheptaheterocyclic ketones **1a** -**1l** with a variety of diverse electron withdrawing or electron donating substituents at ortho, meta or para positions of the two phenyl rings, the corresponding (*R*)-dibenzoheterocyclic alcohols were obtained with high yields and excellent enantioselectivities. For oxa-cyclic substrate**1m** -**1o** , the reaction worked well to produce**2m** -**2o** with 95%-99% yield and 90%->99% ee. The absolute configuration of chiral compound **2a** was unambiguously confirmed by X-ray Diffraction analysis (CCDC number: 2221153). We speculated that the remaining products **2** of ATH follow the same trend by analogy.

Scheme 2 Substrate scope of the reaction

To demonstrated the synthetic potential of the current reaction, gram-scale experiment of asymmetric transfer hydrogenation of**1a** was conducted with a substrate catalyst ratio of 1000/1, and >99% yield and >99% ee of **2a** were achieved, which could be further transformed to baloxavir in just one step (Scheme 3).

Scheme 3 Gram-scale experiment

Conclusions

In conclusion, we have developed a highly practical and enantioselective rhodium-catalyzed asymmetric transfer hydrogenation of dibenzoheptaheterocyclic ketones with high activities and excellent enantioselectivities under mild reaction conditions. With this method, we had achieved the asymmetric reduction of a series of dibenzoheptaheterocyclic ketones, and the corresponding chiral alcohols have been obtained with 75%-99% yield and 90-99% ee. Significantly, this study provided a facile method for the asymmetric reduction of difluorodibenzo[*b,e*]thiepin-11(6H)-one **1a** to prepare the key chiral intermediate of baloxavir marboxil, synthetical potential of the current reaction has been demonstrated by the gram-scale amplification experiment with retention of yield and enantioselectivity with a substrate catalyst ratio of 1000/1.

Experimental

Representative procedure for the rhodium-catalysed asymmetric transfer hydrogenation: To a vial were added **1a** (66 mg, 0.25 mmol, 1.0 equiv.), **Cat6** (0.005 equiv., S/C = 200), and the solution of formic acid/DBU (1:1) (3.0 equiv) in dried THF (5 mL), under argon atmosphere. The mixture was stirred at room temperature for 24 hours. After the reaction was complete, the solvent was removed at reduced pressure, the resulting mixture was dissolved in ethyl acetate and then washed for 2 times with water, the combined organic layer was separated and concentrated at reduced pressure. Then the crude product was purified by silica gel column chromatography to give the pure product **2a** with 99% yield and 99% ee. The enantiomeric excess was determined by HPLC on chiral IA column via gradient elution method, 254 nm, 25 °C, *n* Hexane: *i* PrOH = 95:5; flow 0.8 mL/min; t_R (major) = 18.38 min, t_R (minor) = 15.80 min. (the HPLC gradient elution method is shown in the Table S1 in the supporting information).

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2023xxxxx.

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Entry for the Table of Contents

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Herein, we have developed a highly practical and enantioselective rhodium-catalyzed asymmetric transfer hydrogenation of