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Highly enantioselective Rh-catalyzed asymmetric reductive dearomatization of multi-nitrogen polycyclic pyrazolo[1,5-*a*]pyrimidines†

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A highly enantioselective rhodium-catalyzed reductive dearomatization of 7-substituted pyrazolo[1,5-*a*]pyrimidines has been realized for the first time by two strategies to afford chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines with excellent enantioselectivities of up to 98% ee. This method also provides an efficient approach for the synthesis of the powerful BTK inhibitor, zanubrutinib.

Introduction

Chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine is an important structural unit, which is prevalent in pharmaceuticals and bioactive molecules.¹ For example, zanubrutinib containing chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine is a new powerful BTK inhibitor that enables a complete and lasting precise inhibition of the BTK target (Fig. 1).² The compound **A** is a potent and selective inhibitor of CDK9, which enables short duration of target engagement for the treatment of hematological malignancies.³ Chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine and its derivatives also play an important role in selective inhibitor and selective KV1.5 blockers such as BMS394136.⁴ Because of this importance, the development of efficient methods for enantioselective synthesis of chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines has attracted considerable attention from chemists.

Although the chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine skeleton is of significance in natural products and pharmaceuticals, there are few methods for enantioselective synthesis of this class of compounds. The approach to chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines mainly relies on chemical or biocatalytic resolution of racemates.⁵ Compared with the resolution method, the transition-metal-catalyzed reductive dearomatization of prochiral substituted pyrazolo

[1,5-*a*]pyrimidines obviously is a straightforward method to prepare chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines. To our surprise, the asymmetric reduction of substituted pyrazolo[1,5-*a*]pyrimidines has not been explored so far. This is perhaps mainly attributed to the following points: (1) the high density of the nitrogen atom which has a strong coordination effect on the poisoning or deactivation of chiral catalysts; (2) the inherent stability of the aromaticity of substrates leading to lower reactivity, and the strict conditions required to break it which will adversely affect the enantioselectivity and chemical selectivity. Generally, low reactivity and poor chemical and stereo selectivity are the main challenges in asymmetric reduction of substituted pyrazolo[1,5-*a*]pyrimidines. In recent years, great efforts have been devoted to asymmetric reduction of polycyclic *N*-heterocyclic compounds⁶ and excellent results have been achieved for pyrrolo[1,2-*a*]pyrazines and their salts,^{7,8} pyrrolo/indolo[1,2-*a*]quinoxalines,⁹ and imidazo[1,2-*a*]pyridines¹⁰ using a chiral iridium–diphosphine complex and ruthenium–NHC complex as the catalysts by Zhou's and Glorius's group, respectively. In the asymmetric hydrogenation of aromatic *N*-heterocyclic compounds, catalyst or/and substrate activation is usually required for good reactivity and enantioselectivity.^{11–14} Although some progress has been made in the hydrogenation of polycyclic nitrogen-containing one or two nitrogen atoms,^{12–14} there are few attempts on the hydrogenation of the polycyclic *N*-

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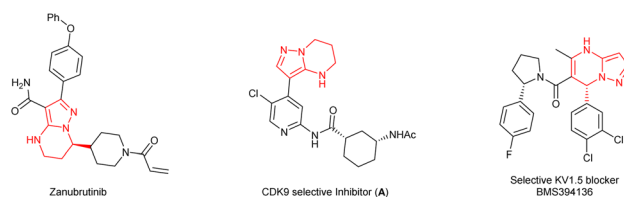
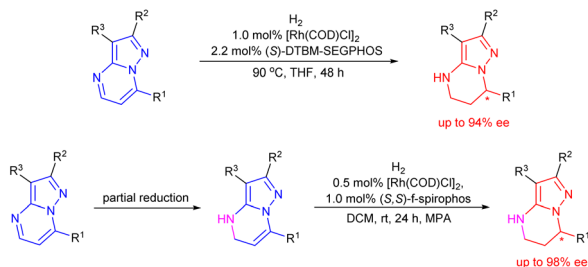


Fig. 1 Examples of drug molecules containing polyheteroatom heteroaromatic structures.





Scheme 1 Rh-catalyzed asymmetric hydrogenation of heteroarenes.

heterocyclic substrates with more nitrogen atoms, that is, higher nitrogen density. The only example is a chiral ruthenium–NHC complex catalyzed enantioselective hydrogenation of 1,2,3-triazolo[1,5-*a*]pyridines with moderate enantioselectivity (up to 66% ee) reported by Glorius and co-workers.¹⁰ Therefore, to develop an efficient catalyst for realization of asymmetric reductive dearomatization of polycyclic *N*-heterocyclic substrates with higher nitrogen density is highly desirable and is of significance for organic and pharmaceutical synthesis. Based on the outstanding work of Zhou and Glorius in the

Table 1 Optimization of reaction conditions for asymmetric hydrogenation of 7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile **1a**^a

Entry	Ligand	Solvent	<i>T</i> (°C)	Conv. ^b	ee ^c
1	L1	THF	60	Trace	—
2	L2	THF	60	Trace	—
3	L3	THF	60	Trace	—
4	L4	THF	60	18	80
5	L5	THF	60	18	86
6	L6	THF	60	Trace	—
7	L7	THF	60	70	91
8	L7	CH ₂ Cl ₂	60	22	92
9	L7	CHCl ₃	60	Trace	—
10	L7	MeOH	60	Trace	—
11	L7	Et ₂ O	60	54	91
12	L7	Toluene	60	42	89
13	L7	THF	80	97	92
14	L7	THF	90	>99	92
15 ^d	L7	THF	90	>99	65
16 ^e	L7	THF	90	>99	92
17 ^f	L7	THF	90	85	91

^a Unless otherwise mentioned, all reactions were carried out with a [Rh(COD)Cl]₂/diphosphine (monophosphine)/substrate = 2.5:5.5:100, 80 atm H₂, 60 °C, 24 h. ^b Determined by GC analysis.

^c Determined by chiral supercritical fluid chromatography (SFC) using a chiral stationary phase. ^d 2.5 mol% [Ir(COD)Cl]₂, 5.5 mol% (*S*)-DTBM-Segphos, 80 atm H₂, 90 °C, 24 h. ^e 1.0 mol% [Rh(COD)Cl]₂, 2.2 mol% (*S*)-DTBM-Segphos, 80 atm H₂, 90 °C, 48 h. ^f 1.0 mol% [Rh(COD)Cl]₂, 2.2 mol% (*S*)-DTBM-Segphos, 60 atm H₂, 90 °C, 48 h.

asymmetric reduction of *N*-heterocyclic arenes¹⁵ and our previous great progress in asymmetric hydrogenation of various substrates,¹⁶ we hence report an asymmetric reductive dearomatization of substituted pyrazolo[1,5-*a*]pyrimidines containing three nitrogen atoms by two strategies without any activation of the catalyst and substrate providing chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines with excellent enantioselectivities of up to 98% ee (Scheme 1).

Results and discussion

In our initial study, 7-phenylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile **1a** was chosen as the model substrate, and hydrogenation was carried out under 80 atm of H₂ in THF at 60 °C for 24 h using the complex of [Rh(COD)Cl]₂ and (*S,S*)-f-Binaphane (**L1**) (Table 1). Disappointingly, the desired product is not obtained under these conditions. Some other bidentate diphosphine ligands (Fig. 2) including (*R,R*)-QuinoxP* (**L2**), (*R,R*)-Me-Duphos (**L3**), (*S*)-Binap (**L4**), (*R*)-Segphos (**L5**) and chiral monophosphorus ligand (*R*)-Monophos (**L6**) were also evaluated (entries 2–6). Although the enantioselectivities could reach 86% ee using **L4** and **L5**, the conversions were too low (entries 4–5). Excitingly, (*S*)-DTBM-Segphos (**L7**) achieved 92% ee with 76% conversion (entry 7). It was found that the solvent had an extremely important influence on the conversion, but had no obvious effect on the enantioselectivity. There was almost no reactivity in MeOH or CHCl₃ (entries 9 and 10). Although good to high enantioselectivities were achieved in CH₂Cl₂, Et₂O and toluene, moderate conversions were obtained (entries 8, 11 and 12). When the temperature increased to 80 °C, the conversion was significantly improved (entry 13). At a higher temperature, 90 °C, the reaction could be accomplished without any erosion of the enantioselectivity (entry 14). When we used [Ir(COD)Cl]₂ and (*S*)-DTBM-Segphos complexes as catalysts, the enantioselectivity decreased to 65% ee despite the full conversion (entry 15). More significantly, even on reducing the catalyst loading to 2 mol%, the hydrogenation could still be completed in 48 h with 92% ee maintained (entry 16). When the hydrogen pressure was reduced to 60 atm, the enantioselectivity remained unchanged, but only 85% conversion was achieved (entry 17).

Inspired by the promising results obtained in the hydrogenation of substrate **1a**, a variety of pyrazolo[1,5-*a*]pyrimidines **1b–1s** were then prepared and evaluated in the hydrogenation under the optimized conditions. To our delight, all of the

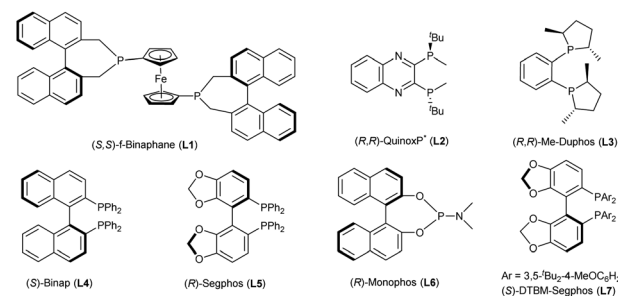
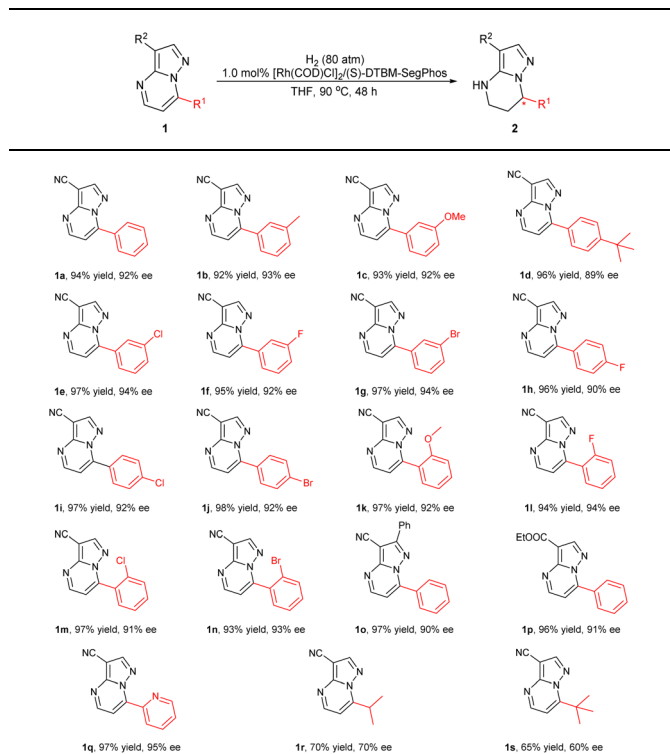
Fig. 2 Structures of chiral phosphine ligands screened for **1a**.

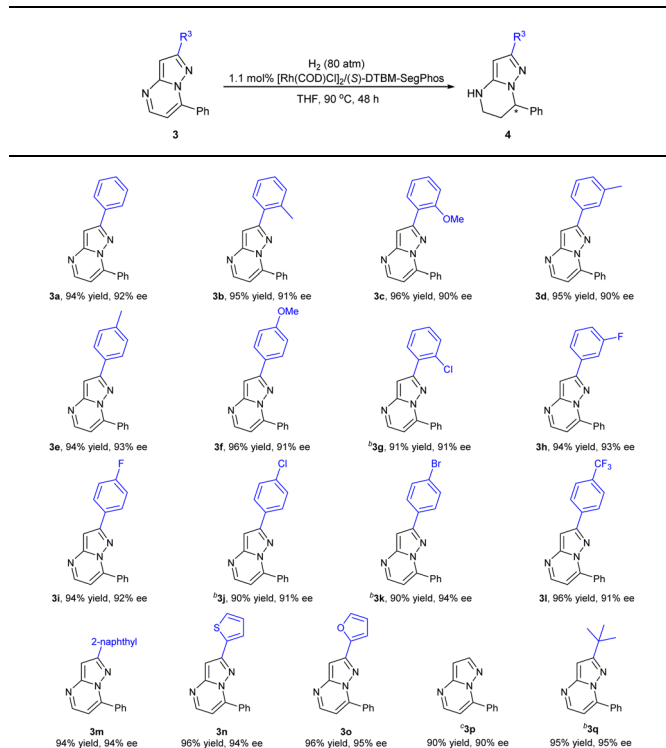
Table 2 Rh-catalyzed asymmetric hydrogenation of prazolo[1,5-a]pyrimidine **1**^a

^a All reactions were carried out with a [Rh(COD)Cl]₂/(S)-DTBM-Segphos/substrate ratio of 1.0:2.2:100, 80 atm of H₂ at 90 °C for 48 h. The conversion was determined by ¹H NMR spectroscopy or GC analysis; enantioselectivity was determined by SFC or HPLC analysis using a chiral stationary phase.

substrates could be successfully hydrogenated to afford the corresponding products **2** in high yields with moderate to excellent enantioselectivities (Table 2). In general, the electronic effect of substituents and the position on the phenyl ring had little influence on the reactivity and enantioselectivity. For instance, the substrates **1b**, **1c** and **1d** bearing an electron-donating substituent including methyl, methoxyl or *t*-butyl groups at the *meta*- or *para*-position of the aryl group provided the products in high yields and enantioselectivities of 89–93% ee. The substrates with electron-withdrawing substituents such as F, Cl and Br groups, could be smoothly hydrogenated to produce the desired chiral products with full conversions and 90–94% ee values (**1e–1j**). The *ortho*-substituted substrates exhibited comparably high reactivity and enantioselectivity (91–94% ee) regardless of the electron-withdrawing or electron-donating substituents (**1k–1n**). The substrate **1o** with a large conjugated system could still be successfully converted into the corresponding product with good yield and enantioselectivity (97% yield, 90% ee). It was found that replacing the cyano group on the heterocycle with an ester group had no effect on the reactivity or enantioselectivity (**1p**). Moreover, the pyridinyl substrate **1q** bearing four nitrogen atoms could exhibit pretty good reactivity and the corresponding hydrogenation product

2q was obtained in 97% yield with 95% ee. However, replacing the phenyl ring at the 7-position with an alkyl group such as isopropyl or *t*-butyl led to a decrease in yields and enantioselectivities (**1r–1s**). This demonstrated that the planarity had a positive effect on the coordination and recognition of the catalyst.

In order to further investigate the substrate scope of the catalyst, we then prepared a variety of 2-substituted substrates **3** and applied them to the hydrogenation under the optimized conditions. Delightedly, all of the substrates examined (**3a–3q**) could be successfully hydrogenated to produce the corresponding chiral heterocyclic compound with good yields and excellent enantioselectivities, 90–95% ee. As shown by the results in Table 3, the enantioselectivity and reactivity were not affected by the electronic properties or the position of the substituent in the phenyl ring. The substrates **3b–3f** with electron-donating substituents (Me and MeO) could be fully hydrogenated to furnish products with pretty good ee values, 90–93% ee. The substrates **3g–3l** with an electron-withdrawing substituent including F, Cl, Br or CF₃ groups could also achieve a high enantioselectivity of 91–94% ee. In addition, the larger sterically hindered 2-naphthyl substrate **3m** also showed

Table 3 Rh-catalyzed asymmetric hydrogenation of pyrazolo[1,5-a]pyrimidine **3**^a

^a All reactions were carried out with a [Rh(COD)Cl]₂/(S)-DTBM-Segphos/substrate ratio of 1.1:2.4:100, 80 atm of H₂ at 90 °C for 48 h. ^b 1.5 mol% [Rh(COD)Cl]₂, 3.3 mol (S)-DTBM-Segphos and 80 atm of H₂ at 90 °C for 48 h. ^c 2.0 mol% [Rh(COD)Cl]₂, 4.4 mol (S)-DTBM-Segphos, 80 atm of H₂ at 90 °C for 48 h. The conversion was determined by ¹H NMR spectroscopy or GC analysis; enantioselectivity was determined by SFC or HPLC analysis using a chiral stationary phase.



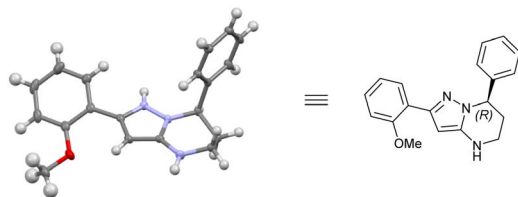


Fig. 3 X-ray crystal structure of product (*R*)-4c.

similar reactivity and enantioselectivity providing 94% ee. It was noteworthy that the substrates bearing a 2-thiophenyl or 2-furanly were also successfully hydrogenated with full conversions and excellent enantioselectivities (94–95% ee). Substrate **3p** without any substituent at the 2-position exhibited relatively lower reactivity despite the similar enantioselectivity and required more amount of catalyst loading for complete conversion. In comparison, the *t*-butyl substituted **3q** with large steric hindrance could achieve full conversion and 95% ee. Perhaps the substituent at the 2-position could prevent poisoning or deactivation of the chiral catalyst due to steric hindrance from the nitrogen in the pyrazole moiety.

Finally, the absolute configuration of the hydrogenation product **4c** was determined and assigned to be the (*R*) configuration by X-ray crystallographic analysis of the corresponding single-crystal structure (Fig. 3).

Alternatively, we further developed the strategy of sequential reduction of pyrazolo[1,5-*a*]pyrimidines for synthesis of chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines. Substrate **1a** was first partially reduced by NaBH₃CN (sodium cyanoborohydride) to produce intermediate **5a**, followed by hydrogenation with a chiral catalyst to finally obtain chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines under mild conditions with this strategy (Scheme 2).

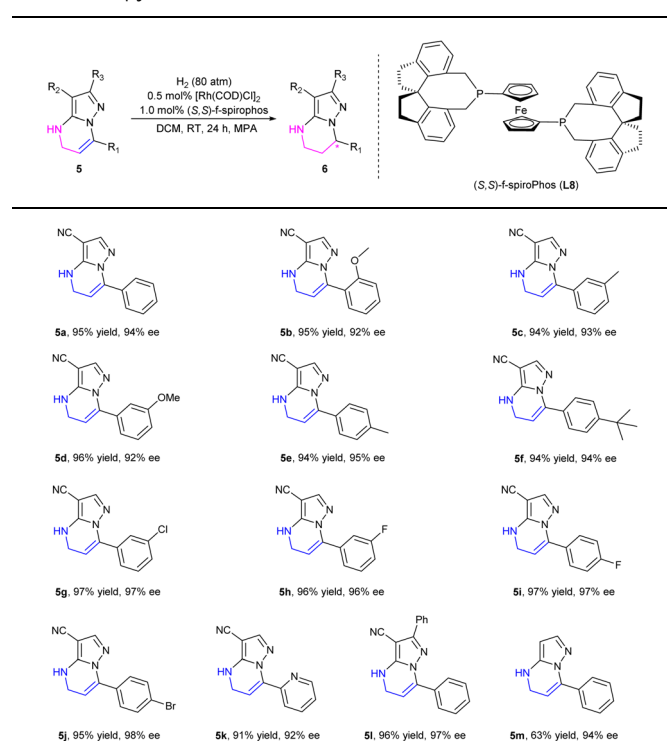
After the optimization of reaction conditions including the screening of chiral ligands, solvents and additives, the substrate 7-phenyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine-3-carbonitrile **5a** could be completely hydrogenated in CH₂Cl₂ at room temperature, catalyzed by the complex of [Rh(COD)Cl]₂ and (*S,S*)-f-spiroPhos to produce **6a** with a higher enantioselectivity of 94% ee in the presence of *N*-methyl-*p*-anisidine (MPA), which could prevent disproportionation.¹⁷

Encouraged by the exciting result achieved in the hydrogenation of substrate **5a**, a variety of 4,5-dihydropyrazolo[1,5-*a*]pyrimidines **5b–5m** were then prepared and evaluated in the hydrogenation under the optimized conditions. The corresponding chiral products **6a–6m** were afforded in high yields with up to 98% ee (Table 4). Generally, the enantioselectivity achieved by the substrates bearing electron-withdrawing



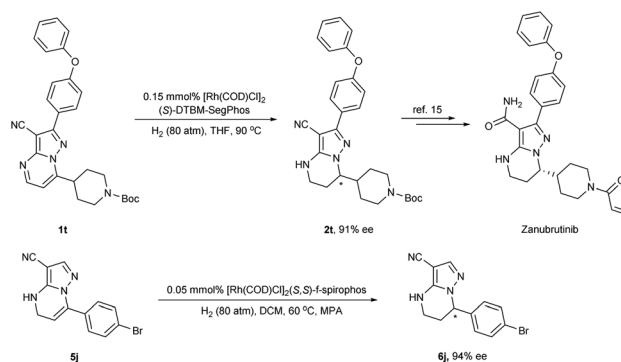
Scheme 2 Sequential reduction of pyrazolo[1,5-*a*]pyrimidines.

Table 4 Rh-catalyzed asymmetric hydrogenation of 4,5-dihydropyrazolo[1,5-*a*]pyrimidine **5a**^a



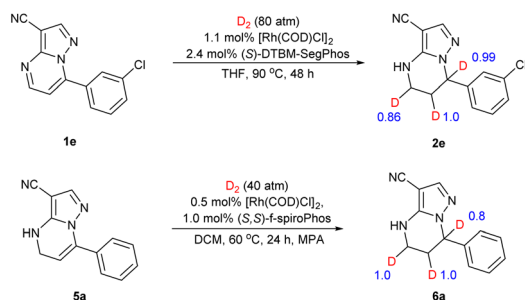
^a All reactions were carried out with a [Rh(COD)Cl]₂/(*S,S*)-f-spiroPhos/substrate/MPA ratio of 0.5 : 1.1 : 100 : 100, DCM and 80 atm of H₂ at rt for 24 h. The conversion was determined by ¹H NMR spectroscopy or GC analysis; enantioselectivity was determined by SFC or HPLC analysis using a chiral stationary phase.

substituents on the phenyl ring was higher than those achieved by substrates with electron-donating substituents. The F-, Cl- or Br-substituted substrates **5g–5j** achieved higher ee values of up to 98%, while the substrates **5b–5f** bearing an electron-donating substituent provided products with 92–95% ee. Notably, the substrates **5k** bearing a pyridine heterocycle and **5l** with larger conjugated substituents could also be smoothly hydrogenated affording the products **6k** and **6l** in high yields and enantioselectivities, 92% and 97% ee, respectively. When



Scheme 3 Catalyst loading experiment and application.





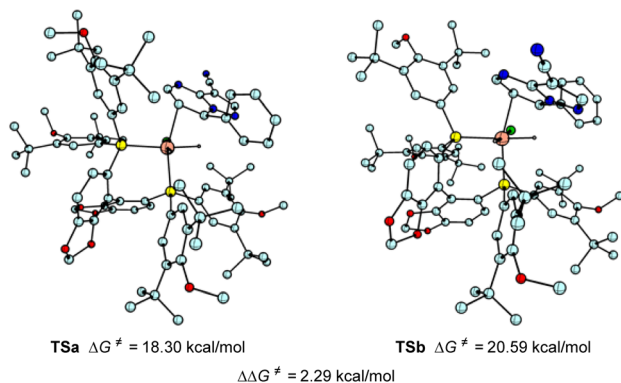
Scheme 4 Deuterium labelling experiments.

substrate **5m** without a substituent at the 2-position was evaluated, only 63% yield was obtained despite achieving similar enantioselectivity (94% ee), which perhaps demonstrated that the substituents at the 2 or 3 position had a positive effect on avoiding the deactivation of the catalyst.

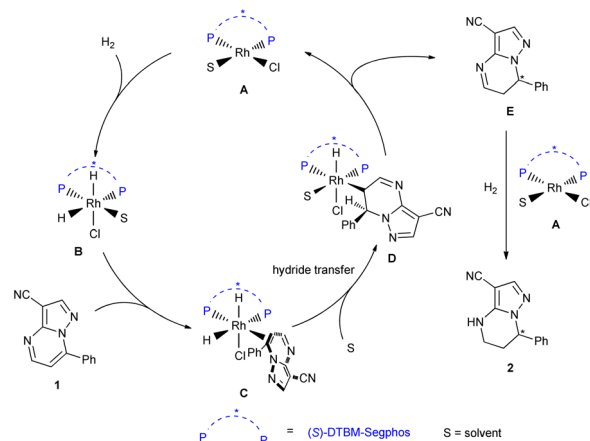
In order to demonstrate the practical utility of this method, we carried out the hydrogenation of substrate **1t** under a lower catalyst loading (Scheme 3). The desired product **2t** could still be obtained in 96% yield with a high enantioselectivity of 91% ee under 0.3 mol% catalyst loading. More significantly, the product **2t** could be used to synthesize the powerful anti-cancer pharmaceutical Zanutrutinib.¹⁸ Furthermore, the hydrogenation of **5j** was also smoothly accomplished using 0.1 mol% catalyst loading ($S/C = 1000$) to afford **6j** in 92% isolated yield with 94% ee.

To gain insight into the possible catalytic mechanism of this asymmetric hydrogenation, deuterium labelling experiments were conducted (Scheme 4). The asymmetric hydrogenation of substrate **1e** was performed under 80 atm of D_2 instead of H_2 in THF. It was found that the 5,6,7-D incorporated deuteration product **2e** was observed. The substrate **5a** also underwent deuterium labelling experiments. The results showed that deuterium substitution occurred at positions 5, 6 and 7 of the substrate.

To probe the origin of the enantioselectivity, density functional theory (DFT) calculations were also performed (Scheme 5). The hydride transfer step which was supposed to be the selectivity determination step in asymmetric hydrogenation¹⁹



Scheme 5 Origin of enantioselectivity.



Scheme 6 Proposed catalytic cycle.

was paid attention. The DFT calculations revealed that the favored *Si*-face coordination of the substrate with rhodium (TSa) led to the formation of the major (*R*) stereoisomer, which is in accordance with the experimental results.

Based on the results of the deuterium labelling experiments, DFT calculations and the literature,¹⁹ we proposed the mechanism of this reaction (Scheme 6). Complex A of rhodium metal and diphosphine ligand first underwent oxidative addition with H_2 to form species B. Then substrate **1** coordinated with B to provide species C, followed by hydride transfer to give the species D. The intermediate E was obtained and the complex A was regenerated by reductive elimination of species D. Finally, the intermediate E could be further hydrogenated to produce the final product **2**.

Conclusions

In conclusion, we realized Rh-catalyzed asymmetric reductive dearomatization of polycyclic pyrazolo[1,5-*a*]pyrimidines with three nitrogen atoms *via* two different strategies to afford chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines with excellent enantioselectivities of up to 98% ee. This method also provided an efficient approach for the synthesis of the powerful BTK inhibitor, zanutrutinib.

Data availability

General experimental procedures, compound characterization data, analysis of enantioselectivities of products and crystal parameters for the compound **4c** are available in the ESI.†

Author contributions

G. H. conceived the idea and directed the project. C. X., G. X., Q. G., and X. W. performed the experiments and the analytical characterization. W. D and G. Z. performed the theoretical calculations and modelling. C. X., G. X., and G. H. wrote the manuscript. All authors discussed the results and commented on the manuscript.



Conflicts of interest

There are no conflicts to declare.

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