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# Iridium-catalyzed asymmetric hydrogenation of quinazolinones†

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Enantioselective hydrogenation of quinazolinones has been successfully realized by employing a chiral iridium/diphosphine complex as catalyst, furnishing the chiral dihydroquinazolinones with excellent yield and up to 98% enantioselectivity. Asymmetric hydrogenation at the gram scale was also conducted smoothly without loss of reactivity and enantioselectivity. Using the above methodology as the key step, the enantiopure bioactive Eg5 inhibitor and (−)-SDZ 267-489 could also be conveniently synthesized.

Chiral dihydroquinazolinones are significant and prevalent substructures in numerous biologically active natural products and pharmaceuticals (Fig. 1).[1] Their promising pharmacological activities such as their antiviral activity, and their use in the treatment of HIV and cardiovascular diseases have attracted the attention of chemists and pharmaceutical researchers.[2] For example, drug candidate DPC 083 is a potent HIV-1 nonnucleoside reverse transcriptase inhibitor.[3] In addition, the $Ca^{2+}/Na^{+}$ ion exchanger inhibitor SM-15811 exhibits potential activity for the treatment of ischemic heart disease.[2c,4] At present, several effective strategies have been developed for the synthesis of chiral dihydroquinazolinones, including aza-Henry reactions,[5] asymmetric Strecker reaction of cyclic ketimines,[6] chiral auxiliary-mediated nucleophilic addition[7] and so on.[8]

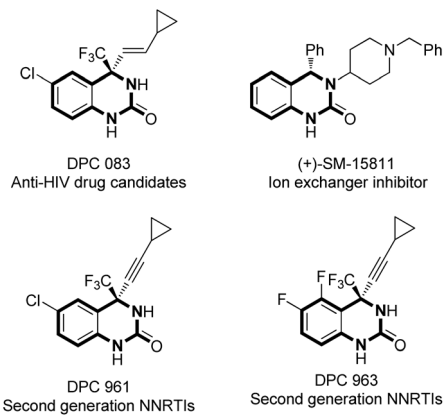
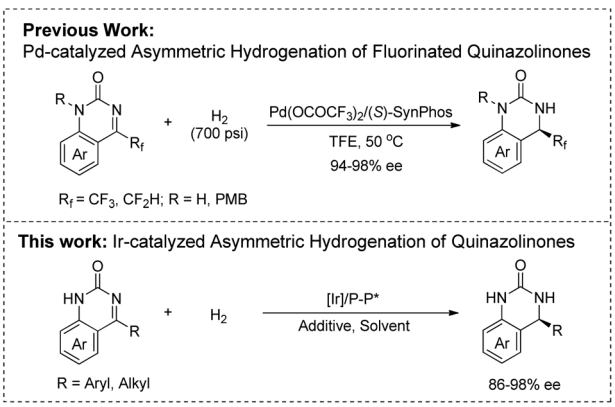



**Fig. 1** Some selected biologically active molecules containing the dihydroquinazolin-2(1*H*)-one motif.

Although chemists have made tireless efforts, efficient catalytic enantioselective methodologies for the construction of structurally diverse dihydroquinazolinones are still highly desirable. According to retrosynthetic analysis, asymmetric hydrogenation of the corresponding quinazolinones should be the most straightforward and atom-economical approach to chiral dihydroquinazolinones. To the best of our knowledge, there has been only one report on palladium-catalyzed asymmetric hydrogenation of fluorinated quinazolinones by Zhou and co-workers. This reaction could proceed smoothly with excellent enantioselectivity, but the substrate scope is restricted to fluorinated quinazolinones (Scheme 1).[9] Thus, the further pursuit of an efficient hydrogenation catalyst




**Scheme 1** Asymmetric hydrogenation of quinazolinones.

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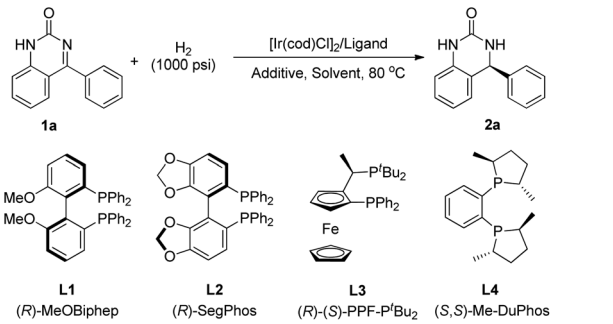
system for this process with general applicability is still highly desirable.

Iridium-catalyzed asymmetric hydrogenation of imines[10,11] and heteroaromatics[12] has been widely and rapidly developed in the past few years. Chiral iridium complex catalysts combined with halogenide additives may also provide great promise for asymmetric hydrogenation of quinazolinones due to the following aspects: first, in general, the halogenide additives in the iridium-catalyzed hydrogenation are often used to improve the reactivity through oxidizing iridium(I) to iridium(III). Second, the hydrogen halide generated *in situ* during the hydrogenation could improve the reactivity *via* accelerating the lactam–lactim tautomerism to be more toward the oxo form, which is similar to the substrate 2-hydroxypyrimidine.[13] Last but not least, the urea motif of the reductive products efficiently decreased the coordination ability with the catalyst. Recently, we also successfully realized the palladium-catalyzed and iridium-catalyzed asymmetric hydrogenation of aromatic 2-hydroxypyrimidines with up to 99% ee.[14] Inspired by these previous works and considering the usefulness of the products, we turned our attention to iridium-catalyzed asymmetric hydrogenation of quinazolinones. Herein, we reported an iridium-catalyzed asymmetric hydrogenation of quinazolinones with up to 98% ee and excellent yields (Scheme 1). Using this methodology as the key step, the enantiopure bioactive Eg5 inhibitor and (−)-SDZ 267-489 could also be conveniently synthesized.

At the outset of our study, 4-phenylquinazolin-2(1*H*)-one **1a** was employed as a model substrate for studying the asymmetric hydrogenation. Initial examinations began with solvent screening. To our delight, in the presence of $[Ir(cod)Cl]_2$/(*R*)-MeOBiphep/$I_2$, the hydrogenation of **1a** was conducted smoothly in dichloromethane (DCM) to furnish the desired product **2a** with 52% ee and full conversion (Table 1, entry 1). A slightly better enantioselectivity was observed in toluene (entry 2). When methanol was used, poor enantioselectivity was observed (entry 3). Solvent screening results revealed that tetrahydrofuran (THF) was the optimal choice, and 77% ee was obtained (entry 4). Encouraged by the above promising result, we next began to investigate additive effects (entries 5–7). Surprisingly, the ee value dramatically increased to 96% ee when BCDMH (1-bromo-3-chloro-5,5-dimethylhydantoin) acted as the halogen source (entry 7). Subsequently, some commercially available chiral diphosphine ligands were also screened to further improve the enantioselectivity (entries 8–10). (*R*)-SegPhos (**L2**) proved to be the best choice with respect to the yield and enantioselectivity, whereas the electron-donating ferrocene-derived Josiphos (**L3**) gave lower enantioselectivity despite having high reactivity. Besides, (*S*,*S*)-Me-DuPhos (**L4**) also only gave 21% ee. When the temperature decreased to 60 °C, the yield and ee value could also be maintained (entry 11). Notably, it was possible to perform the reaction at an even lower temperature (25 °C) and slightly lower hydrogen pressure (600 psi). The results showed that the reaction proceeded well without deterioration of the conversion and enantioselectivity (entry 12). Thus, the optimized reaction conditions were established: $[Ir(cod)Cl]_2$/(*R*)-SegPhos/BCDMH/THF/25 °C/600 psi $H_2$.

**Table 1** The evaluation of reaction parameters[a]

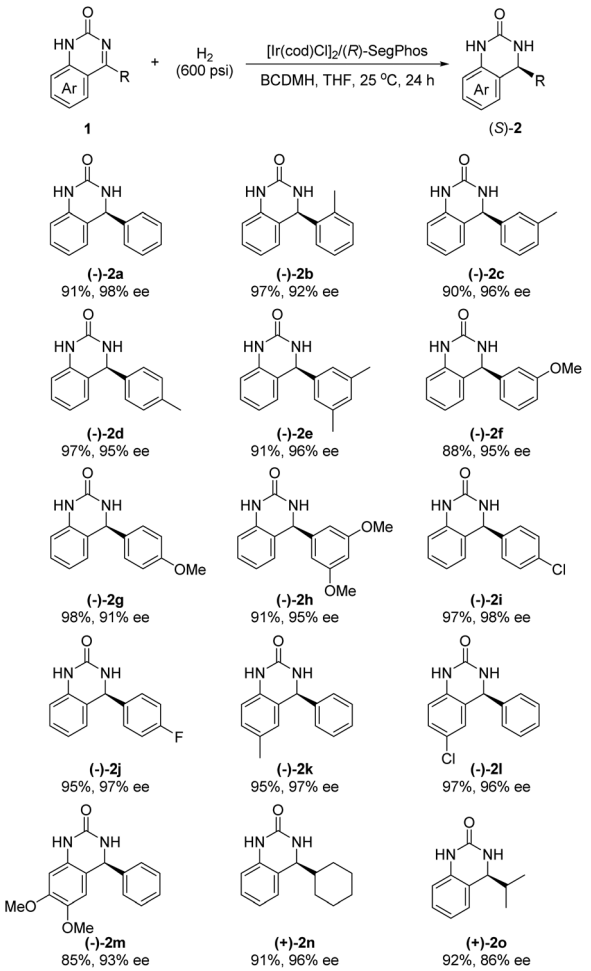



| Entry | Solvent | Additive | Ligand | ee[b] (%) |
|---|---|---|---|---|
| 1 | DCM | $I_2$ | **L1** | 52 |
| 2 | PhMe | $I_2$ | **L1** | 66 |
| 3 | MeOH | $I_2$ | **L1** | 4 |
| 4 | THF | $I_2$ | **L1** | 77 |
| 5 | THF | NIS | **L1** | 69 |
| 6 | THF | NBS | **L1** | 95 |
| 7 | THF | BCDMH | **L1** | 96 |
| 8 | THF | BCDMH | **L2** | 97 |
| 9 | THF | BCDMH | **L3** | 1 |
| 10 | THF | BCDMH | **L4** | 21 |
| 11[c] | THF | BCDMH | **L2** | 97 |
| 12[d] | THF | BCDMH | **L2** | 98 |

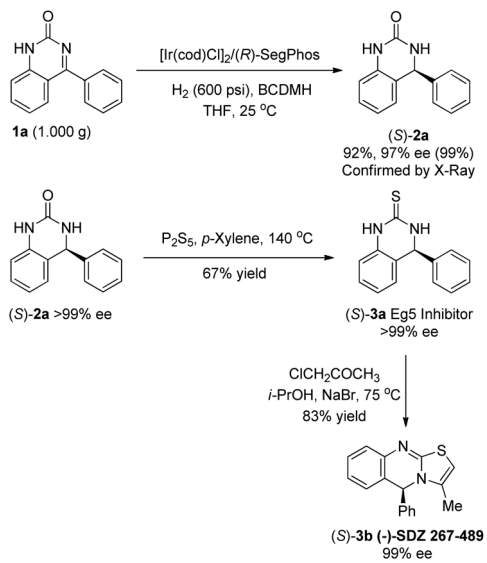
[a] Reaction conditions: **1a** (0.2 mmol), $[Ir(cod)Cl]_2$ (1 mol%), ligand (2.2 mol%), additive (10 mol%), $H_2$ (1000 psi), solvent (3.0 mL), 80 °C, 24 h, if not otherwise noted. All the conversions were >95%, which was determined by $^1$H NMR analysis. [b] Determined by HPLC analysis. [c] 60 °C. [d] 25 °C, $H_2$ (600 psi). NIS: *N*-iodosuccinimide, NBS: *N*-bromosuccinimide, BCDMH: 1-bromo-3-chloro-5,5-dimethyl imidazolidine-2,4-dione.

With the optimal conditions in hand, we sought to explore the asymmetric hydrogenation of a wide array of quinazolinone substrates (Scheme 2). As expected, a diverse array of substrates could be hydrogenated very well under the standard reaction conditions, giving the corresponding chiral products in high enantioselectivities and yields. Firstly, the quinazolinones bearing a variety of substituted aromatic rings were examined. The reaction was not sensitive to the steric hindrance effect of the substituent on the phenyl rings (**2b** *vs.* **2c**). Electron-donating as well as electron-withdrawing groups at the *para*-position of the phenyl ring of substrate **1** were very compatible, delivering the corresponding chiral products in high yields and enantioselectivities (**2b–2j**). It was noted that the yields and ee values were not decreased when methyl and the halide Cl groups were introduced on the left aromatic ring (**2k** and **2l**). However, introducing a strong electron-donating methoxyl substituent on the quinazolinone core resulted in slightly lower enantioselectivity (**2m**). In addition, alkyl (cyclohexyl and isopropyl) substituted quinazolinones could perform smoothly, giving the chiral products (**2n**) and (**2o**) with 96% ee and 86% ee, respectively.

Moreover, to further highlight the practicality of this methodology, the hydrogenation at the gram scale was conducted, giving the desired product in 92% yield and 97% ee (Scheme 3) without loss of reactivity and enantioselectivity.




**Scheme 2** Substrate scope. Conditions: **1** (0.2 mmol), $[Ir(cod)Cl]_2$ (1 mol%), (*R*)-Segphos (2.2 mol%), BCDMH (10 mol%), $H_2$ (600 psi), THF (3.0 mL), 25 °C, 24 h.




**Scheme 3** Gram scale experiment and synthesis of bioactive Eg5 inhibitor and (–)-SDZ 267-489.

The ee can be upgraded to 99% after a simple recrystallization with diethyl ether and dichloromethane (for details, see ESI†). The absolute configuration of the product **2a** was unambiguously assigned to be *S* by X-ray crystallographic analysis.

Human Eg5 is a mitotic kinesin, which plays an important role in the formation and maintenance of bipolar spindles during mitosis. 4-Phenyl-3,4-dihydroquinazoline-2(1*H*)-thione (*S*)-**3a** could be used as a potent Eg5 inhibitor.[15] Chiral thiourea (*S*)-**3a** could be conveniently synthesized by a simple one-step reaction. Furthermore, SDZ 267-489 is a serum HDL cholesterol raising agent.[16] To obtain enantiopure compounds, the previous report used the resolution method with D-tartaric acid. Here we report the direct synthesis of the chiral compound (*S*)-SDZ 267-489 *via* two steps from (*S*)-**2a** without notable loss of optical purity.

## Conclusion

In conclusion, we have successfully developed an efficient and convenient route to a variety of chiral dihydroquinazolinones with excellent yields and optical purity (up to 98% ee) through the iridium-catalyzed asymmetric hydrogenation of quinazolinones. Additionally, the asymmetric hydrogenation at the gram scale was also conducted smoothly with high reactivity and excellent enantioselectivity. Bioactive compounds including Eg5 inhibitor and (–)-SDZ 267-489 could be synthesized *via* simple steps without notable loss of enantioselectivity. More investigations on enantioselective transformations of other related heteroaromatic compounds are currently ongoing in our laboratory.

## Experimental

### A typical procedure for the asymmetric hydrogenation of quinazolinone 1a

A mixture of $[Ir(cod)Cl]_2$ (1.3 mg, 0.002 mmol) and ligand (*R*)-SegPhos (2.8 mg, 0.0044 mmol) in tetrahydrofuran (1.0 mL) was stirred at room temperature for 10 min in a nitrogen-filled glove box, then BCDMH (4.8 mg, 0.02 mmol) and substrate **1a** (0.2 mmol) together with tetrahydrofuran (2.0 mL) were added, and the mixture was stirred for 10 min. The hydrogenation was performed at 25 °C under hydrogen (600 psi) in a stainless steel autoclave for 24 h. After carefully releasing the hydrogen gas, saturated aqueous sodium bicarbonate (3.0 mL) was added, and stirred for 10–15 min. The mixture was extracted with dichloromethane three times and the combined organic extract was dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated *in vacuo* and further purification was performed by a silica gel column with dichloromethane/methanol (50/1) as eluent to give the chiral product (*S*)-**2a** as white solid (91% yield, 98% ee). The enantiomeric excess was determined by HPLC (OD-H column, *n*-hexane/i-PrOH = 90/10, 1.0 mL $min^{-1}$, 254 nm, 30 °C, $t_1$ = 16.0 min (major), $t_2$ = 24.4 min).

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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