

Accepted Article

Title: Biomimetic Asymmetric Reduction of Quinazolinones with Chiral and Regenerable NAD(P)H Models

Authors: Zi-Biao Zhao, Xiang Li, Bo Wu, and Yong-Gui Zhou*

This manuscript has been accepted and appears as an Accepted Article online.

This work may now be cited as: *Chin. J. Chem.* **2020**, *38*, 10.1002/cjoc.202000045.

The final Version of Record (VoR) of it with formal page numbers will soon be published online in Early View: <http://dx.doi.org/10.1002/cjoc.202000045>.

Biomimetic Asymmetric Reduction of Quinazolinones with Chiral and Regenerable NAD(P)H Models

Zi-Biao Zhao,^a Xiang Li,^a Bo Wu,^a and Yong-Gui Zhou*,^{a,b}

^a State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China.

^b State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China.

Cite this paper: *Chin. J. Chem.* 2019, 37, XXX–XXX. DOI: 10.1002/cjoc.201900XXX

Summary of main observation and conclusion: A facile approach to chiral dihydroquinazolinone derivatives has been described *via* biomimetic asymmetric reduction of quinazolinones with chiral and regenerable NAD(P)H models. The utility of this method was demonstrated by a concise synthesis of the bromodomain protein divalent inhibitor.

Background and Originality Content

Dihydroquinazolinones are identified as significant and prevalent structural motifs in bioactive and pharmaceutical molecules.^[1] It is well known that these molecules could be served as agonists, inhibitors, and antitumor agents. In addition, these molecules also possess a wide variety of pharmacological activities such as antiviral, antibacterial and antimalarial activity (Figure 1).^[1] For example, a series of dihydroquinazolinone derivatives have been used as selective M1 and M4 muscarinic acetylcholine receptors agonist.^[1f] They could also be used as sodium/calcium exchanger inhibitor^[1e,j] (II) and PDE7 inhibitor (III).^[1f,g] Bromodomain protein divalent inhibitor (IV) with antitumor activity^[1m] has the core structure towards the dihydroquinazolinones.

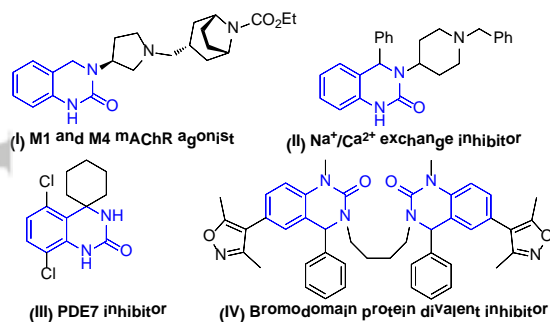


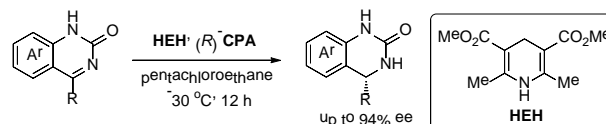
Figure 1 Bioactive molecules containing the dihydroquinazolinone motifs.

Owing to the remarkable importance of dihydroquinazolinones, a variety of powerful approaches have been developed for the synthesis of dihydroquinazolinones including organocatalytic aza-Henry reaction,^[2] Mannich reaction,^[3] organocatalytic Strecker reaction,^[4] allylic C-H amination,^[5] decarboxylative [4+2] cycloaddition^[6] and other reactions.^[7] Apart from these methods, asymmetric hydrogenation of easy available quinazolinones would be one straightforward and atom- economical way for

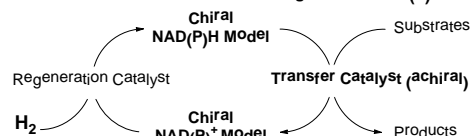
synthesis of chiral dihydroquinazolinones. In 2013, Zhou, Ma and co-workers^[8] reported palladium-catalyzed asymmetric hydrogenation of the fluorinated quinazolinones, providing the chiral products with excellent enantioselectivity. Subsequently, Zhou and coworkers^[9] developed an iridium-catalyzed asymmetric hydrogenation of quinazolinones. This method has a broad scope of substrates, excellent yields and up to 98% enantioselectivities. Despite the above advance, it is still necessary to develop new and effective approaches to the optically active dihydroquinazolinones.

Scheme 1 Biomimetic asymmetric reduction of quinazolinones.

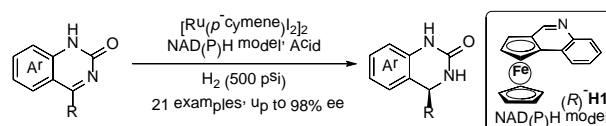
a) Asymmetric transfer hydrogenation with stoichiometric HEH by Shi¹³



b) Biomimetic reduction with chiral and regenerable NAD(P)H models



c) This work: Biomimetic asymmetric reduction of quinazolinones



- * Catalytic amount of NAD(P)H models
- * Broad substrates scope
- * Commercially available acids
- * Mild reaction conditions

Biomimetic asymmetric reduction (BMAR) has attracted much attention and gradually become one of the most important choices. NADP/NADPH couple^[10] driven reduction reactions have

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/cjoc.202000045

also been studied in recent years. A series of NAD(P)H models were designed and utilized.^[11] In these models, the most representative example is Hantzsch esters (HEH).^[12] In 2019, Shi's group reported a chiral phosphoric acid catalyzed asymmetric transfer hydrogenation of quinazolinones with HEH as hydrogen atom donor (Scheme 1).^[13] However, this reaction required the stoichiometric amount of models and suffered from restriction on regeneration, leading to low atomic economy. The regeneration of the consumed models will also bring many benefits such as increasing conversion and omitting NAD(P)H models separation from the complex system. Due to the importance of regeneration of models, researchers have invested great scientific interest in the regeneration of NAD(P)H models.^[14] Recently, our group reported the synthesis of chiral and regenerable NAD(P)H models based on the planar-chiral ferrocene and their application in biomimetic asymmetric reduction of tetrasubstituted olefins and imines.^[15] Inspired by this work, we envisaged that biomimetic asymmetric reduction of quinazolinones with regenerable and chiral NAD(P)H models would be another straightforward approach for synthesis of chiral dihydroquinazolinones. Herein, we present biomimetic asymmetric reduction of quinazolinones, giving the chiral products with high yields and up to 98% ee. The utility of this method was demonstrated by a concise synthesis of the bromodomain protein divalent inhibitor.

Results and Discussion

Initially, we investigated background reaction with ruthenium catalyst $[\text{Ru}(p\text{-cymene})\text{I}_2]_2$ (Table 1, entry 1). This reaction barely gave the desired product in low 17% conversion. The conversion could be slightly improved using the chiral and regenerable NAD(P)H models without transfer catalysts (entry 2). Delightedly, the biomimetic asymmetric reduction performed smoothly using commercially available simple Brønsted acid as transfer catalyst, giving the desirable product in 88% enantioselectivity and full conversion (entry 3). Meanwhile, when we increased the amount of Brønsted acid, no obvious improvement in enantioselectivity was observed (entry 4). Urea catalysts which are capable of activating substrates through hydrogen-bonding activation have received significant attention. Unfortunately, the biomimetic reduction reaction could not give the satisfied result (entry 5).

Table 1 Initial result on biomimetic reduction of quinazolinones.^a

entry	transfer catalysts	NAD(P)H models	conv. (%) ^b	ee (%) ^c
1	--	--	17	--
2	--	(R)-H1	25	2

3 ^d	Brønsted acid	(R)-H1	>95	88
4 ^e	Brønsted acid	(R)-H1	>95	89
5 ^f	Urea catalyst	(R)-H1	10	43

^a Conditions: **1a** (0.10 mmol), $[\text{Ru}(p\text{-cymene})\text{I}_2]_2$ (0.5 mol%), NAD(P)H models (10 mol%), EtOAc (2.0 mL), H_2 (500 psi), 35 °C, 24 h. ^b Measured by analysis of ^1H NMR. ^c Determined by chiral HPLC. ^d Brønsted acid (5 mol%). ^e Brønsted acid (10 mol%). ^f Urea catalyst (20 mol%), CHCl_3 (2.0 mL).

Subsequently, we turned our attention to screening of the transfer catalyst Brønsted acids. A series of Brønsted acids were evaluated (Table 2, entries 1-5). In case of the acid-2 with electron-withdrawing nitro group, a high conversion and 88% ee were observed (entry 2). Next, the solvent effects were examined with acid-2. Initially, full conversion and moderate enantioselectivity could be obtained in THF (entry 6). When the solvents was changed to the toluene, the reaction could provide the target product in 92% ee and full conversion (entry 7). It was worth noting that solvent trifluorotoluene was the best choice in terms of conversion and enantioselectivity (entry 8). In addition, *t*-butyl methyl ether and chloroform were also proved to be beneficial for enantiocontrol (entries 9 and 11). When acetonitrile was used as solvent, no desired product was observed (entry 10).

Table 2 The evaluation of reaction parameters.^a

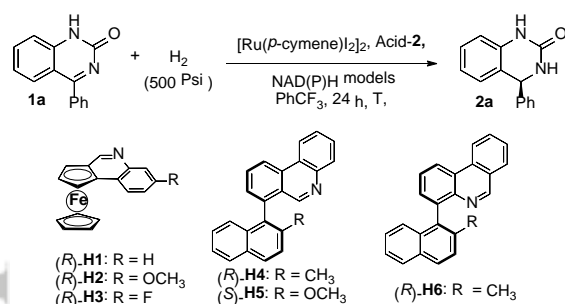
entry	Brønsted acid	solvent	conv. (%) ^b	ee (%) ^c
1	Acid-1	EtOAc	70	34
2	Acid-2	EtOAc	>95	88
3	Acid-3	EtOAc	79	29
4	Acid-4	EtOAc	27	3
5	Acid-5	EtOAc	>95	77
6	Acid-2	THF	>95	58
7	Acid-2	Toluene	>95	92
8	Acid-2	PhCF_3	>95	95
9	Acid-2	$t\text{-BuOMe}$	>95	90
10	Acid-2	CH_3CN	<5	--
11	Acid-2	CHCl_3	>95	91

^a Conditions: **1a** (0.10 mmol), $[\text{Ru}(p\text{-cymene})\text{I}_2]_2$ (0.5 mol%), (R)-H1 (10 mol%), Brønsted acid (5 mol%), solvent (2.0 mL), H_2 (500 psi), 35 °C, 24 h. ^b Measured by analysis of ^1H NMR. ^c Determined by chiral HPLC.

Next, we conducted the reaction with different kinds of chiral and regenerable NAD(P)H models (Table 3). The reaction gave the better result with NAD(P)H models with planar chirality. When electron-donating group such as methoxy was introduced, the expected product could be obtained in 93% ee (entry 2). Compared to the electron-donating group, electron-withdrawing group obviously slowed down the reduction reaction, affording the product in low 38% conversion and moderate 79% ee (entry 3). In addition, the NAD(P)H models with axial chirality proved to be ineffective in terms of reactivity and enantioselectivity (entries 4–6). To our delight, when the temperature was decreased to 25 °C, full conversion and 96% ee were still obtained. Thus, the optimized conditions were established as: substrate quinazolinone **1a** (0.20 mmol), [Ru(*p*-cymene)₂]₂ (0.5 mol%), (*R*)-**H1** (10 mol%), acid-**2** (5 mol%), H₂ (500 psi), PhCF₃, 25 °C, 24 h.

After optimizing the reaction conditions, substrate generality was investigated (Table 4). Firstly, the effect of methyl group on the different positions of 4-phenyl on the enantioselectivity and reactivity was screened, all performed very well with 93–95% ee (**2b–2d**). When the methyl group was replaced with more electron-donating group such as methoxy group, slightly lower 90% ee was achieved (**2e**). Similar result was also observed with electron-withdrawing fluorine group (**2f**). Notably, disubstituted substrates obviously affected the enantioselectivity and yield (**2g–2h**). For the 4-biphenylquinazolinone (**1i**), moderate 73% yield and 85% ee was obtained. For the 4-naphthylquinazolinone (**1j**), the desirable product was obtained moderate 67% yield and 90% ee. For the alkyl substituted substrates, high yields were obtained, albeit with moderate enantioselectivities (**2k–2l**).

Table 3 The evaluation of NAD(P)H models.^a



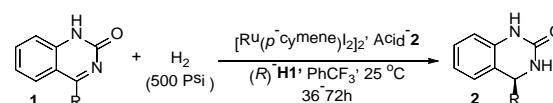
entry	NAD(P)H models	conv. (%) ^b	ee (%) ^c
1	(<i>R</i>)- H1	>95	95
2	(<i>R</i>)- H2	>95	93
3	(<i>R</i>)- H3	38	79
4	(<i>R</i>)- H4	70	31
5	(<i>S</i>)- H5	>95	6
6	(<i>R</i>)- H6	14	5
7 ^d	(<i>R</i>)- H1	>95	96

^a Conditions: **1a** (0.10 mmol), [Ru(*p*-cymene)₂]₂ (0.5 mol%), NAD(P)H model (10 mol%), PhCF₃ (2.0 mL), H₂ (500 psi), 35 °C, 24 h. ^b Measured by

analysis of ¹H NMR. ^c Determined by chiral HPLC. ^d 25 °C.

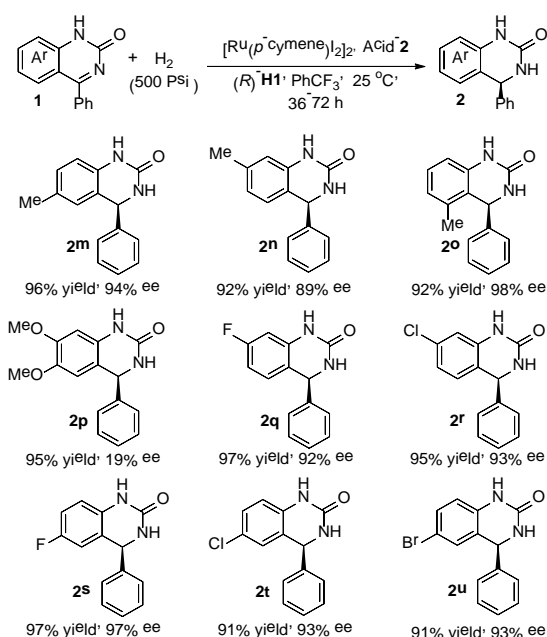
To further demonstrate the generality of our method, we explored the substrate scope of different substituents on the benzo ring (Scheme 2). It was worth noting that methyl group on the different positions of the basic skeleton could deliver the products with high yields and 89%–98% ee (**2m–2o**). Dimethoxy substituted substrates could lead to excellent yield, albeit with low 19% of enantioselectivity (**2p**). The reason might ascribe to electronic effect. A series of electron-withdrawing substrates performed very well in the optimized conditions (**2q–2u**). Halogen group at different positions had marginal effect on reactivities and enantioselectivities (**2s–2u**). The halogen group could provide more opportunities for further transformations.

Table 4 Substrate scope.^a



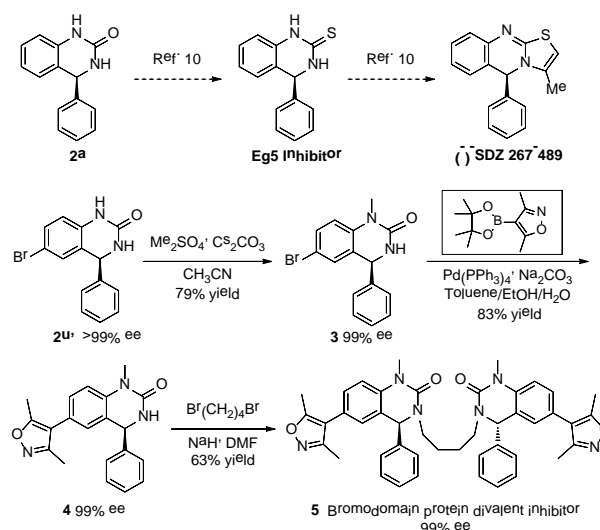
entry	R	yield (%) ^b	ee (%) ^c
1	Ph	94 (2a)	95
2	2-MeC ₆ H ₄	90 (2b)	93
3	3-MeC ₆ H ₄	96 (2c)	93
4	4-MeC ₆ H ₄	96 (2d)	94
5	4-MeOC ₆ H ₄	92 (2e)	90
6	4-FC ₆ H ₄	97 (2f)	88
7	3,5-Me ₂ C ₆ H ₃	46 (2g)	85
8	3,5-(MeO) ₂ C ₆ H ₃	<5 (2h)	–
9	4-PhC ₆ H ₄	73 (2i)	85
10	Naphthyl	67 (2j)	90
11	Cyclohexyl	91 (2k)	74
12	Isopropyl	87 (2l)	73

^a Conditions: **1** (0.20 mmol), [Ru(*p*-cymene)₂]₂ (0.5 mol%), (*R*)-**H1** (10 mol%), acid-**2** (5 mol%), PhCF₃ (2.0 mL), H₂ (500 psi), 25 °C, 36–72 h. ^b Isolated yields. ^c Determined by chiral HPLC.

Scheme 2 Substrate scope^a

^a Conditions: **1** (0.20 mmol), $[Ru(p\text{-cymene})I_2]_2$ (0.5 mol%), (*R*)-**H1** (10 mol%), acid-**2** (5 mol%), $PhCF_3$ (2.0 mL), H_2 (500 psi), 25 °C, 36-72 h. ^b Isolated yields. ^c Determined by chiral HPLC.

A plausible mechanism for biomimetic asymmetric reduction was proposed,^[15b] firstly, chiral NAD(P)H model (*R*)-**H1** could be *in situ* reduced with hydrogen by ruthenium complex. Subsequently, the reduced chiral NAD(P)H model could realize biomimetic asymmetric reduction of quinazolinones in the presence of Brønsted acid. Meanwhile, the chiral NAD(P)H model (*R*)-**H1** was regenerated for the next catalytic cycle.

Scheme 3 The synthesis of three pharmaceutically active molecules^a

To further demonstrate synthetic utility of this methodology, three pharmaceutically active molecules containing dihydroquinazolinone motifs could be concisely synthesized (Scheme 3). For instance, human potent Eg5 inhibitor^[16] and a serum HDL cholesterol raising agent such as SDZ 267-489^[17], which play considerable role in human physical activity. The above two bioactive molecules could be formally synthesized in simple one or two steps from chiral dihydroquinazolinones (**2a**). In addition, bromodomain protein divalent inhibitors could interfere the combination with the Brd 4 and acetylated histones.^[1m] The inhibitors (*S,S*)-**5** have the core structure towards the dihydroquinazolinones. Hence, the bromodomain protein divalent inhibitors (*S,S*)-**5** could be conveniently synthesized from the dihydroquinazolinones (**2u**) through three steps (*N*-methylation, Suzuki coupling and dialkylation) with good yields and without loss of optical purity.

Conclusions

In summary, we have developed a facile and efficient protocol that enables the synthesis of chiral dihydroquinazolinones with excellent enantioselectivities and high yields through biomimetic asymmetric reduction. This biomimetic method employs chiral and regenerable NAD(P)H models and commercially available achiral Brønsted acid as transfer catalysts under the mild reaction conditions. Furthermore, this methodology provides a concise approach to synthesize the pharmaceutically active molecules such as the bromodomain protein divalent inhibitor. Further development of these chiral and regenerable NAD(P)H models in other biomimetic catalytic reactions are under investigation by our group, and will be reported in due course.

Experimental

General procedure for biomimetic asymmetric reduction of quinazolinone: A mixture of $[Ru(p\text{-cymene})I_2]_2$ (1.0 mg, 0.001 mmol), Brønsted acid acid-**2** (3.4 mg 0.01 mmol), NAD(P)H model

(*R*)-**H1** (5.7 mg, 0.02 mmol) and quinazolinones **1** (0.20 mmol) in trifluorotoluene (3.0 mL) was stirred at room temperature for 5 min in glove box and then the mixture was transferred to an autoclave. The reduction was performed at room temperature under hydrogen gas (500 psi) for 36–72 h. After careful release of hydrogen gas, the autoclave was opened and the reaction mixture was directly purified by column chromatography on silica gel using dichloromethane/methanol as eluent to give the desired products **2**. The enantiomeric excesses were determined by chiral HPLC.

The full experimental details can be found in the Supporting Information

Supporting Information

The supporting information for this article is available on the WWW under <https://doi.org/10.1002/cjoc.2018xxxxx>.

Acknowledgement

Financial support from the National Natural Science Foundation of China (21532006, 21690074) and Chinese Academy of Sciences (XDB17020300, QYZDJ-SSW-SLH035) is acknowledged.

References

- [1] For reviews see: (a) Hemalatha, K.; Madhumitha, G. Synthetic Strategy with Representation on Mechanistic Pathway for the Therapeutic Applications of Dihydroquinazolinones. *Eur. J. Med. Chem.* **2016**, *123*, 596–630. For selected examples, see: (b) Tucker, T. J.; Lyle, T. A.; Wiscourt, C. M.; Britcher, S. F.; Young, S. D.; Sanders, W. M.; Lumma, W. C.; Goldman, M. E.; O'Brien, J. A.; Ball, R. G.; Homnick, C. F.; Schleif, W. A.; Emini, E. A.; Huff, J. R.; Anderson, P. S. Synthesis of a Series of 4-(Arylethynyl)-6-chloro-4-cyclopropyl-3,4-dihydroquinazolin-2(1H)-ones as Novel Non-nucleoside HIV-1 Reverse Transcriptase Inhibitors. *J. Med. Chem.* **1994**, *37*, 2437–2444. (c) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Jeffrey, S.; Bacheler, L. T.; Klabe, R. M.; Diamond, S.; Lai, C.-M.; Rabel, S. R.; Saye, J. A.; Adams, S. P.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. Expanded-Spectrum Nonnucleoside Reverse Transcriptase Inhibitors Inhibit Clinically Relevant Mutant Variants of Human Immunodeficiency Virus Type 1. *Antimicrob. Agents Chemother.* **1999**, *43*, 2893–2897. (d) Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Logue, K.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. Inhibition of Clinically Relevant Mutant Variants of HIV-1 by Quinazolinone Non-Nucleoside Reverse Transcriptase Inhibitors. *J. Med. Chem.* **2000**, *43*, 2019–2030. (e) Hasegawa, H.; Muraoka, M.; Matsui, K.; Kojima, A. Discovery of A Novel Potent Na⁺/Ca²⁺ Exchanger Inhibitor: Design, Synthesis and Structure–activity Relationships of 3,4-dihydro-2(1H)-quinazolinone Derivatives. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3471–3475. (f) Lorthiois, E.; Bernardelli, P.; Vergne, F.; Oliveira, C.; Mafroud, A.; Proust, E.; Heuze, L.; Moreau, F.; Idrissi, M.; Tertre, A.; Bertin, B.; Coupe, M.; Wrigglesworth, R.; Descours, A.; Soulard, P.; Berna, P. Spiroquinazolinones as Novel, Potent, and Selective PDE7 Inhibitors. Part 1. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4623–4626. (g) Bernardelli, P.; Lorthiois, E.; Vergne, F.; Oliveira, C.; Mafroud, A.; Proust, E.; Pham, N.; Ducrot, P.; Moreau, F.; Idrissi, M.; Tertre, A.; Bertin, B.; Coupe, M.; Chevalier, E.; Descours, A.; Berlioz-Seux, F.; Berna, P.; Li, M. Spiroquinazolinones as Novel, Potent, and Selective PDE7 Inhibitors. Part 2: Optimization of 5,8-disubstituted Derivatives. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4627–4631. (h) Hasegawa, H.; Muraoka, M.; Ohmori, M.; Matsui, K.; Kojima, A. A Novel Class of Sodium/Calcium Exchanger Inhibitor: Design, Synthesis, and Structure–activity Relationships of 3,4-dihydro-2(1H)-quinazolinone Derivatives. *Bioorg. Med. Chem.* **2005**, *13*, 3721–3735. (i) Hasegawa, H.; Muraoka, M.; Ohmori, M.; Matsui, K.; Kojima, A. Design, Synthesis, and Structure–Activity Relationships of 3,4-Dihydropyridopyrimidin-2(1H)-one Derivatives as a Novel Class of Sodium/Calcium Exchanger Inhibitor. *Chem. Pharm. Bull.* **2005**, *53*, 1236–1239. (j) Hasegawa, H.; Muraoka, M.; Matsui, K.; Kojima, A. A Novel Class of Sodium/Calcium Exchanger Inhibitors: Design, Synthesis, and Structure–activity Relationships of 4-phenyl-3-(piperidin-4-yl)-3,4-dihydro-2(1H)-quinazolinone Derivatives. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 727–730. (k) Daga, P. R.; Doerksen, R. J. Stereoelectronic Properties of Spiroquinazolinones in Differential PDE7 Inhibitory Activity. *J. Comput. Chem.* **2008**, *29*, 1945–1954. (l) Uruno, Y.; Konishi, Y.; Suwa, A.; Takai, K.; Tojo, K.; Nakako, T.; Sakai, M.; Enomoto, T.; Matsuda, H.; Kitamura, A.; Sumiyoshi, T. Discovery of Dihydroquinazolinone Derivatives as Potent, Selective, and CNS-penetrant M1 and M4 Muscarinic Acetylcholine Receptors Agonists. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5357–5361. (m) Zhou, J.; Zhang, H.; Yang, Y.; Zhao, L.; Zhang, J.; Li, X.; Wu, Z. *CN107056771*, **2017**.
- [2] Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. Bifunctional Cinchona Alkaloid Thiourea Catalyzed Highly Efficient, Enantioselective Aza-Henry Reaction of Cyclic Trifluoromethyl Ketimines: Synthesis of Anti-HIV Drug DPC 083. *Angew. Chem. Int. Ed.* **2011**, *50*, 11773–11776.
- [3] Yuan, H.-N.; Wang, S.; Nie, J.; Meng, W.; Yao, Q.; Ma, J.-A. Hydrogen-Bond-Directed Enantioselective Decarboxylative Mannich Reaction of β -Ketoacids with Ketimines: Application to the Synthesis of Anti-HIV Drug DPC 083. *Angew. Chem. Int. Ed.* **2013**, *52*, 3869–3873.
- [4] Zhang, F.-G.; Zhu, X.-Y.; Li, S.; Nie, J.; Ma, J.-A. Highly Enantioselective Organocatalytic Strecker Reaction of Cyclic *N*-acyl trifluoromethylketimines: Synthesis of Anti-HIV drug DPC 083. *Chem. Commun.* **2012**, *48*, 11552–11554.
- [5] Wang, P.-S.; Shen, M.-L.; Wang, T.-C.; Lin, H.-C.; Gong, L.-Z. Access to Chiral Dihydropyrimidines through Palladium-Catalyzed Asymmetric Allylic C–H Amination. *Angew. Chem. Int. Ed.* **2017**, *56*, 16032–16036.
- [6] Lu, Y.-N.; Lan, J.-P.; Mao, Y.-J.; Wang, Y.-X.; Mei, G.-J.; Shi, F. Catalytic Asymmetric *de novo* Construction of Dihydroquinazolinone Scaffolds via Enantioselective Decarboxylative [4+2] Cycloadditions. *Chem. Commun.* **2018**, *54*, 13527–13530.
- [7] (a) Huffman, M. A.; Yasuda, N.; Decamp, A. E.; Grabowski, E. J. J. Lithium Alkoxides of Cinchona Alkaloids as Chiral Controllers for Enantioselective Acetylide Addition to Cyclic *N*-Acyl Ketimines. *J. Org. Chem.* **1995**, *60*, 1590–1594. (b) Magnus, N. A.; Confalone, P. N.; Storace, L. A New Asymmetric 1,4-addition Method: Application to the Synthesis of the HIV Non-nucleoside Reverse Transcriptase Inhibitor DPC 961. *Tetrahedron Lett.* **2000**, *41*, 3015–3019. (c) Kauffman, G. S.; Harris, G. D.; Dorow, R. L.; Stone, B. R. P.; Parsons Jr, R. L.; Pesti, J. A.; Magnus, N. A.; Fortunak, J. M.; Confalone, P. N.; Nugent, W. A. An Efficient Chiral Moderator Prepared from Inexpensive (+)-3-Carene: Synthesis of the HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitor DPC 963. *Org. Lett.* **2000**, *2*, 3119–3121. (d) Magnus, N. A.; Confalone, P. N.; Storace, L.; Patel, M.; Wood, C. C.; Davis, W. P.; Parsons Jr, R. L. General Scope of 1,4-Diastereoselective

- Additions to a 2(3H)-Quinazolinone: Practical Preparation of HIV Therapeutics. *J. Org. Chem.* **2003**, *68*, 754-761. (e) Jiang, B.; Si, Y.-G. Highly Enantioselective Construction of a Chiral Tertiary Carbon Center by Alkynylation of a Cyclic N-Acyl Ketimine: An Efficient Preparation of HIV Therapeutics. *Angew. Chem., Int. Ed.* **2004**, *43*, 216-218. (f) Xie, H.; Song, A.; Zhang, X.; Chen, X.; Li, H.; Sheng, C.; Wang, W. Quinine-thiourea catalyzed Enantioselective Hydrophosphonylation of Trifluoromethyl 2(1H)-quinazolinones. *Chem. Commun.* **2013**, *49*, 928-930. (g) Sawant, R. T.; Stevens, M. Y.; Odell, L. R. Microwave-Assisted aza-Friedel-Crafts Arylation of N-Acyliminium Ions: Expedient Access to 4-Aryl 3,4-Dihydroquinazolinones. *ACS Omega*. **2018**, *3*, 14258-14265.
- [8] Duan, Y.; Zhu, X.-Y.; Ma, J.-A.; Zhou, Y.-G. Palladium-catalyzed Asymmetric Hydrogenation of Fluorinated Quinazolinones. *Tetrahedron Lett.* **2013**, *54*, 6161-6163.
- [9] Feng, G.-S.; Zhao, Z.-B.; Shi, L.; Zhou, Y.-G. Iridium-catalyzed Asymmetric Hydrogenation of Quinazolinones. *Org. Chem. Front.* **2019**, *6*, 2250-2253.
- [10] For reviews see: (a) Gebicki, J.; Marcinek, A.; Zielonka, J. Transient Species in the Stepwise Interconversion of NADH and NAD⁺. *Acc. Chem. Res.* **2004**, *37*, 379-386. (b) Houtkooper, R. H.; Cantó, C.; Wanders, R. J.; Auwerx, J. The Secret Life of NAD⁺: An Old Metabolite Controlling New Metabolic Signaling Pathways. *Endocr. Rev.* **2010**, *31*, 194-223. (c) Lin, H. Nicotinamide Adenine Dinucleotide: Beyond A Redox Coenzyme. *Org. Biomol. Chem.* **2007**, *5*, 2541-2554. (d) Wu, H.; Tian, C.; Song, X.; Liu, C.; Yang, D.; Jiang, Z. Methods For the Regeneration of Nicotinamide-coenzymes. *Green Chem.* **2013**, *15*, 1773-1789.
- [11] (a) Ohnishi, Y.; Kagami, M.; Ohno, A. Reduction by A Model of NAD(P)H. Effect of Metal Ion and Stereochemistry on the Reduction of Alpha-keto esters by 1,4-dihyronicotinamide Derivatives. *J. Am. Chem. Soc.* **1975**, *97*, 4766-4768. (b) Kanomata, N.; Nakata, T. A Compact Chemical Miniature of a Holoenzyme, Coenzyme NADH Linked Dehydrogenase. Design and Synthesis of Bridged NADH Models and Their Highly Enantioselective Reduction. *J. Am. Chem. Soc.* **2000**, *122*, 4563-4568. (c) Wang, N.-X.; Zhao, J. Progress in Coenzyme NADH Model Compounds and Asymmetric Reduction of Benzoylformate. *Synlett* **2007**, *18*, 2785-2791. (d) Bai, C.-B.; Wang, N.-X.; Xing, Y.; Lan, X.-W. Progress on Chiral NAD(P)H Model Compounds. *Synlett* **2017**, *28*, 402-414.
- [12] For reviews see: (a) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. Enantioselective Organocatalytic Transfer Hydrogenation Reactions using Hantzsch Esters. *Acc. Chem. Res.* **2007**, *40*, 1327-1339. (b) Rueping, M.; Dufour, J.; Schoepke, F. R. Advances in Catalytic Metal-free Reductions: From Bio-inspired Concepts to Applications in the Organocatalytic Synthesis of Pharmaceuticals and Natural Products. *Green Chem.* **2011**, *13*, 1084-1105. (c) Zheng, C.; You, S.-L. Transfer Hydrogenation with Hantzsch Esters and Related organic Hydride Donors. *Chem. Soc. Rev.* **2012**, *41*, 2498-2518. (d) Phillips, A. M. F.; Pombeiro, A. J. L. Recent Advances in Organocatalytic Enantioselective Transfer Hydrogenation. *Org. Biomol. Chem.* **2017**, *15*, 2307-2340.
- [13] Meng, F.-J.; Shi, L.; Jiang, W.-F.; Feng, G.-S.; Lu, X.-B.; Zhao, Z.-B. Chiral Phosphoric Acid-catalyzed Asymmetric Transfer Hydrogenation of Quinazolinones. *Tetrahedron Lett.* **2019**, *60*, 150947-150951.
- [14] For selected examples, see: (a) Lo, H. C.; Fish, R. H. Biomimetic NAD⁺ Models for Tandem Cofactor Regeneration, Horse Liver Alcohol Dehydrogenase Recognition of 1,4-NADH Derivatives, and Chiral Synthesis. *Angew. Chem. Int. Ed.* **2002**, *41*, 478-481. (b) Xu, H.-J.; Liu, Y.-C.; Fu, Y.; Wu, Y.-D. Catalytic Hydrogenation of α,β -Epoxy Ketones to Form β -Hydroxy Ketones Mediated by an NADH Coenzyme Model. *Org. Lett.* **2006**, *8*, 3449-3451. (c) Procuranti, B.; Connon, S. J. A Reductase-mimicking Thiourea Organocatalyst Incorporating A Covalently Bound NADH Analogue: Efficient 1,2-diketone Reduction with in Situ Prosthetic Group Generation and Recycling. *Chem. Commun.* **2007**, 1421-1423. (d) Chen, Q.-A.; Chen, M.-W.; Yu, C.-B.; Shi, L.; Wang, D.-S.; Yang, Y.; Zhou, Y.-G. Biomimetic Asymmetric Hydrogenation: In Situ Regenerable Hantzsch Esters for Asymmetric Hydrogenation of Benzoxazinones. *J. Am. Chem. Soc.* **2011**, *133*, 16432-16435. (e) Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. Dihydrophenanthridine: A New and Easily Regenerable NAD(P)H Model for Biomimetic Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2012**, *134*, 2442-2448. (f) Lu, L.-Q.; Li, Y.; Junge, K.; Beller, M. Iron-Catalyzed Hydrogenation for the In Situ Regeneration of an NAD(P)H Model: Biomimetic Reduction of α -Keto- α -Iminoesters. *Angew. Chem. Int. Ed.* **2013**, *52*, 8382-8386. (g) Chen, Z.-P.; Chen, M.-W.; Guo, R.-N.; Zhou, Y.-G. 4,5-Dihydropyrrolo-[1,2-a]quinoxalines: A Tunable and Regenerable Biomimetic Hydrogen Source. *Org. Lett.* **2014**, *16*, 1406-1409. (h) Lu, L.-Q.; Li, Y.; Junge, K.; Beller, M. Relay Iron/Chiral Brønsted Acid Catalysis: Enantioselective Hydrogenation of Benzoxazinones. *J. Am. Chem. Soc.* **2015**, *137*, 2763-2768. (i) Chen, M.-W.; Wu, B.; Chen, Z.-P.; Shi, L.; Zhou, Y.-G. Synthesis of Chiral Fluorinated Propargylamines via Chemoselective Biomimetic Hydrogenation. *Org. Lett.* **2016**, *18*, 4650-4653. (j) Zhao, L.; Wei, J.; Lu, J.; He, C.; Duan, C. Renewable Molecular Flasks with NADH Models: Combination of Light-Driven Proton Reduction and Biomimetic Hydrogenation of Benzoxazinones. *Angew. Chem. Int. Ed.* **2017**, *56*, 8692-8696.
- [15] (a) Wang, J.; Zhu, Z.-H.; Chen, M.-W.; Chen, Q.-A.; Zhou, Y.-G. Catalytic Biomimetic Asymmetric Reduction of Alkenes and Imines Enabled by Chiral and Regenerable NAD(P)H Models. *Angew. Chem. Int. Ed.* **2019**, *58*, 1813-1817. (b) Wang, J.; Zhao, Z.-B.; Zhao, Y.; Luo, G.; Zhu, Z.-H.; Luo, Y.; Zhou, Y.-G. Chiral and Regenerable NAD(P)H Models Enabled Biomimetic Asymmetric Reduction: Design, Synthesis, Scope, and Mechanistic Studies. *J. Org. Chem.* **2020**, *85*, 2355-2368.
- [16] Sarli, V.; Huemmer, S.; Sunder-Plassmann, N.; Mayer, T. U.; Giannis, A. Synthesis and Biological Evaluation of Novel Eg5 Inhibitors. *ChemBioChem*. **2005**, *6*, 2005-2013.
- [17] Xu, D.; Mattner, P. G.; Kucero, A.; Prasad, K.; Repic, O. An Efficient Synthesis of Enantiopure SDZ 267-489 via A Resolution/racemization Method *Tetrahedron: Asymmetry* **1996**, *7*, 747-754.

(The following will be filled in by the editorial staff)

Manuscript received: XXXX, 2019

Manuscript revised: XXXX, 2019

Manuscript accepted: XXXX, 2019

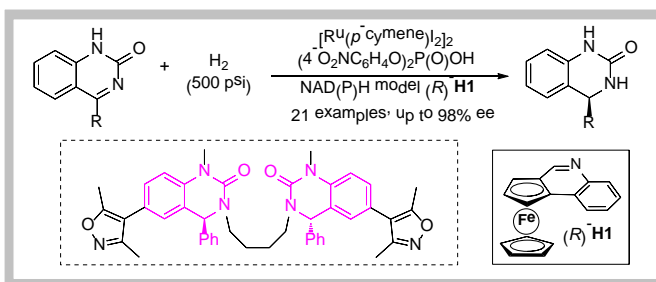
Accepted manuscript online: XXXX, 2019

Version of record online: XXXX, 2019

Entry for the Table of Contents

Page No.

Biomimetic Asymmetric Reduction of Quinazolinones with Chiral and Regenerable NAD(P)H Models



A novel and efficient approach to access chiral dihydroquinazolinone derivatives with excellent enantioselectivities and high yields *via* biomimetic reduction with chiral and regenerable NAD(P)H models has been described. Using the above methodology as the key step, the bromodomain protein divalent inhibitor could be concisely synthesized.

Li-Biao Zhao, Xiang Li, Bo Wu, and Yong-Gui Zhou