Asymmetric Catalysis

Ru-NHC-Catalyzed Asymmetric Hydrogenation of 2-Quinolones to Chiral 3,4-Dihydro-2-Quinolones

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Dedicated to Professor Dieter Hoppe on the occasion of his 80th birthday

Abstract: Direct enantioselective hydrogenation of unsaturated compounds to generate chiral three-dimensional motifs is one of the most straightforward and important approaches in synthetic chemistry. We realized the Ru(II)-NHC-catalyzed asymmetric hydrogenation of 2-quinolones under mild reaction conditions. Alkyl-, aryl- and halogen-substituted optically active dihydro-2-quinolones were obtained in high yields with moderate to excellent enantioselectivities. The reaction provides an efficient and atom-economic pathway to construct simple chiral 3,4-dihydro-2-quinolones. The desired products could be further reduced to tetrahydroquinolines and octahydroquinolones.

Dihydroquinolones, which widely exist in natural products and marketed pharmaceuticals, are known as a class of important heterocycles and exhibit significant biological activities.[1] For example, aripiprazole (antipsychotic drug), carteolol (non-selective beta blocker), vesnarinone (cardiotonic agent), cilostazol (phosphodiesterase-3 inhibitor), as well as melosuavne[1c,g] are drugs or medically useful natural products which all contain the 3,4-dihydro-2-quinolone motif (Scheme 1). In addition, dihydroquinolones could potentially become versatile intermediates which could be further transformed to several other common heterocycles such as tetrahydroquinolines[2] or octahydroquinolones.[3]

Although several methods have been explored to form achiral and racemic dihydroquinolones,[4] the construction of optically active dihydroquinolones, especially dihydro-2-quinolones, is still rare and highly desirable. Currently, there are two main approaches to access chiral dihydro-2-quinolones. The first one is transition-metal-catalyzed asymmetric conjugate addition,[5] however, most examples are focusing on arylation.[6] In 2019, Harutyunyan[6] explored asymmetric alkylation using Grignard reagents to form alkyl-substituted dihydro-2-quinolones, although harsh conditions and limited scope remain an issue due to low activity of 2-quinolone (Scheme 2a). Alternatively, Cao,[7] Gong,[8] and Xiao[9] developed an asymmetric [4+2] cycloaddition to form the above-mentioned motifs. Again, specific functional groups, such as vinyl or ethynyl, are required (Scheme 2b). Thus, developing a more general and atom-economic approach to synthesize simple dihydro-2-quinolones is highly demanding.

Direct hydrogenation of quinolone derivatives to generate dihydroquinolone-containing bioactive molecules is one of the most straightforward and atom-economic approaches and thus has the potential to be applied in large-scale...
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Table 1: Optimization of the reaction conditions.[a]

| Entry | R          | Solvent | Conversion [%][b] | e.r.[c] |
|-------|------------|---------|------------------|---------|
| 1     | H (1a)     | n-hexane| –                | –       |
| 2     | Me (1b)    | n-hexane| >99              | 93:7    |
| 3     | Me (1b)    | toluene | >99              | 90.5:9.5|
| 4     | Me (1b)    | THF     | >99              | 90.5:9.5|
| 5     | Me (1b)    | Et₂O    | >99              | 94:6    |
| 6     | Me (1b)    | i-AmOH   | >99              | 82:18   |
| 7     | Me (1b)    | Et₂O    | >99              | 94:6    |
| 8     | Me (1b)    | Et₂O    | >99              | 94:6    |
| 9     | Me (1b)    | Et₂O    | >99              | 94:6    |

[a] General conditions: [Ru(COD)(2-methylallyl)] (0.01 mmol), KOtBu (0.025 mmol), (R,R)-SNPE·HBF₄ (0.02 mmol) were stirred at 70°C in n-hexane (0.33 mL) for 16 h, after which it was added to 1a or 1b (0.2 mmol) in solvent (1 mL), and the hydrogenation was performed at 25°C under 70 bar H₂ for 24 h. [b] Determined by GC–MS. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction run under 40 bar H₂. [e] Reaction run under 10 bar H₂. [f] The reaction was performed at 15°C.

synthesis.[10] Surprisingly, direct asymmetric hydrogenation of 2-quinolones, especially simple 2-quinolones to dihydroquinolones, has rarely been realized.[11] Hydrogenation of 2-quinolones is hampered by the low reactivity of cyclic α,β-conjugated amides[12] and the poisoning effect of the nitrogen atoms.[12] Undoubtedly, achieving this goal would remove a huge obstacle in the discovery of potential drug targets.

Promisingly, several privileged asymmetric hydrogenation catalyst systems have emerged during the past decades.[13] Among these powerful catalysts, the Ru–NHC complex developed by our group exhibited excellent performance for the hydrogenation of many heteroarenes and nonaromatic cyclic olefins.[14] Inspired by our previous work, we achieved the direct asymmetric hydrogenation of 2-quinolones using our Ru–NHC catalyst (Scheme 2c).

We started our study with commercial substrate 1a. An initial experiment was conducted under 70 bar H₂ in hexane at room temperature (Table 1). Unfortunately, no desired product was detected (Table 1, entry 1). According to our group’s previous work, unprotected quinolone 1a would tautomerize to quinolin-2-ol, which is more stable.[14] Another possible reason would be the poisoning effect of the free amide group on the catalyst.[12] Then, methyl-protected substrate 1b was tested (Table 1, entry 2). We were pleased to find that the reaction occurred smoothly and gave the desired product with 93:7 e.r. We subsequently screened solvents and pressure (Table 1, entries 3–8) and found that the enantiomeric ratio increased slightly to 94:6 when the reaction was performed in diethyl ether (Table 1, entry 7). H₂ pressure had no effect on the yield and enantioselectivity (Table 1, entry 8). Finally, the enantiomeric ratio was improved to 95:5 when the temperature was decreased to 15°C (Table 1, entry 9).

With the optimized condition in hand, we investigated the substrate scope of the reaction. When the protecting group was changed to a benzyl group, the desired product was isolated in 98% yield with 95:5 e.r. (2c). Then, the influence of the substituent in 6-position was studied. As shown in Scheme 3, when methyl or longer alkyl chains were introduced, the corresponding products were obtained in high yields and excellent enantioselectivities (2d–f). Halogen substituents were also tolerated in this catalytic system, giving the products (2g, 2h) smoothly in good enantiomeric ratios. Remarkably, dehalogenated byproduct was not detected. It is worth noting that when methoxy as an electron-donating group was introduced, the e.r. value was increased to 97:3 (2i). We postulate that although the methoxy in 6-position seems far from the olefin, it still has influence on the electronic property of the reduced double bond. Additionally, aryl-substituted products 2j, 2k were also obtained smoothly with e.r. values up to 98:2.

To our delight, if these substitutions were moved to the 7-position, the alkyl (1l, 1m), phenyl (1l, 1u), and halogen substrates (1o–1q) could be reduced successfully with high yield and excellent enantioselectivity. The bromo and chloro compounds (2p, 2q) would be useful building blocks for further manipulation. We also investigated substitutions in 5- and 8-positions. With a methyl substituent in the 5-position, the enantioselectivity of the corresponding product 2s decreased. A remarkable motif in bioactive molecules 2v was obtained in 99% yield with high enantioselectivity,[11] which demonstrates this strategy’s potential in pharmaceutical synthesis. In addition, the absolute configuration of 2v was determined to be R by X-ray crystallographic analysis.[15]

Next, we turned our attention to the impact of substituent groups in the 4-position (Scheme 4). Ethyl-substituted substrate 1w was hydrogenated to the corresponding product (2w) with full conversion and moderate enantiomeric ratio (77:23). Surprisingly, sterically even more demanding substrates 1x and 1y gave the desired products with excellent yields and better enantimeric excess compared to 1w.[16] Interestingly, 3-methyl-substituted product 2u is the key motif of D₂/5-HT₂R receptor dual antagonist SIPI 6360,[15] which could be hydrogenated from the corresponding quinolone in moderate yield under our mild standard conditions.

To demonstrate the utility of this reaction, the products were further manipulated. The dihydro-2-quinolone 2b could be further reduced to tetrahydroquinoline 3b using DIBAL–H as reductant without loss in enantiomeric excess (Scheme 5).[20] More impressively, the dimethyl-substituted product 2v was smoothly transformed to the saturated octahydroquinolone 4r using the Rh–CAAC/H₂ catalyst system.[16,17]

In summary, the first ruthenium-NHC-catalyzed asymmetric hydrogenation of 2-quinolones to simple 3,4-dihydro-2-quinolines has been developed with high yields (up to 99%) and moderate to excellent enantioselectivities (up to 98:2 e.r.). This method shows good functional group compatibility. Alkyl, methoxy, aryl, halogens, and trifluoromethyl...
were tolerated under the mild conditions. Additionally, 3,4-dihydro-2-quinolone derivatives could be further reduced to other interesting chiral three-dimensional motifs. We anticipate that this newly developed procedure would fulfill its potential in the synthesis of building blocks and pharmaceutical compounds.

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Conflict of Interest

The authors declare no conflict of interest.

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[1] a) G. Leclerc, G. Marciniak, N. Decker, J. Schweitz, J. Med. Chem. 1986, 29, 2427 – 2432; b) S. Teramoto, M. Tanaka, H. Shimizu, T. Fujisaka, F. Tabusa, T. Imazumii, K. Yoshida, H. Fujiki, T. Mori, T. Sumida, M. Tominaga, J. Med. Chem. 2003, 46, 3033 – 3044; c) C.-Y. An, X.-M. Li, H. Luo, C.-S. Li, M.-H. Wang, G.-M. Xu, B.-G. Wang, J. Nat. Prod. 2013, 76, 1896 – 1901; d) R. D. Taylor, M. MacCoss, A. D. G. Lawson, J. Med. Chem. 2014, 57, 5845 – 5895; e) X.-W. Chen, Y. Liu, X.-Q. Jin, Y.-Y. Sun, S.-L. Gu, L. Fu, J.-Q. Li, Org. Process Res. Dev. 2016, 20, 1662 – 1667; f) X. Cao, Y. Zhang, Y. Chen, Y. Qiu, M. Yu, X. Xu, X. Lin, B.-F. Liu, L. Zhang, G. Zhang, J. Med. Chem. 2018, 61, 10017 – 10039; g) D. H. El-Kashef, G. Daletos, M. Plenker, R. Hartfeld, A. Mandl, T. Kurtan, H. Weber, W.-P. Deng, Org. Lett. 2019, 21, 4250 – 4259.

[2] a) Y. Kim, E. Shin, P. Beak, Y.-S. Park, Synthesis 2001, 35, 5611 – 5615; b) S. Teramoto, M. Tanaka, H. Watanabe, J. Med. Chem. 2005, 48, 3563 – 3567; c) D. H. El-Kashef, G. Daletos, M. Plenker, R. Hartfeld, A. Mandl, T. Kurtan, H. Weber, W.-P. Deng, Org. Lett. 2019, 21, 4250 – 4259.

[3] a) G. A. Kraus, S. Kesavan, Angew. Chem. Int. Ed. 2005, 44, 12177 – 12179; b) J. J. Verendel, O. Pamies, M. Dieguez, Org. Lett. 2012, 14, 3803 – 3806; c) N. Ortega, D.-T. D. Tang, S. Urban, D. Zhao, F. Glorius, Angew. Chem. Int. Ed. 2013, 52, 9500; d) Angew. Chem. 2013, 125, 18082 – 18088; e) J.-H. Jin, H. Wang, Z.-T. Yang, W.-L. Yang, W. Tang, W.-P. Deng, Org. Lett. 2018, 20, 104 – 107.

[4] a) J. Wu, Z.-B. Zhang, J. Org. Chem. 2017, 82, 4968 – 9472; b) J.-F. Paquin, C. R. J. Stephenson, C. Defeiber, E. M. Carreira, Org. Lett. 2005, 7, 3821 – 3824; c) J. Zhang, Z. Qureshi, L. Sonaglia, M. Lautens, Angew. Chem. Int. Ed. 2014, 53, 13850 – 13853; d) Angew. Chem. 2014, 126, 14070 – 14073.

[5] a) J. Wu, Z.-B. Zhang, J. Org. Chem. 2017, 82, 4968 – 9472; b) J.-F. Paquin, C. R. J. Stephenson, C. Defeiber, E. M. Carreira, Org. Lett. 2005, 7, 3821 – 3824; c) J. Zhang, Z. Qureshi, L. Sonaglia, M. Lautens, Angew. Chem. Int. Ed. 2014, 53, 13850 – 13853; d) Angew. Chem. 2014, 126, 14070 – 14073.

[6] a) J.-F. Paquin, C. R. J. Stephenson, C. Defeiber, E. M. Carreira, Org. Lett. 2005, 7, 3821 – 3824; c) J. Zhang, Z. Qureshi, L. Sonaglia, M. Lautens, Angew. Chem. Int. Ed. 2014, 53, 13850 – 13853; d) Angew. Chem. 2014, 126, 14070 – 14073.

[7] a) J. Wu, Z.-B. Zhang, J. Org. Chem. 2017, 82, 4968 – 9472; b) J.-F. Paquin, C. R. J. Stephenson, C. Defeiber, E. M. Carreira, Org. Lett. 2005, 7, 3821 – 3824; c) J. Zhang, Z. Qureshi, L. Sonaglia, M. Lautens, Angew. Chem. Int. Ed. 2014, 53, 13850 – 13853; d) Angew. Chem. 2014, 126, 14070 – 14073.

[8] a) J. Wu, Z.-B. Zhang, J. Org. Chem. 2017, 82, 4968 – 9472; b) J.-F. Paquin, C. R. J. Stephenson, C. Defeiber, E. M. Carreira, Org. Lett. 2005, 7, 3821 – 3824; c) J. Zhang, Z. Qureshi, L. Sonaglia, M. Lautens, Angew. Chem. Int. Ed. 2014, 53, 13850 – 13853; d) Angew. Chem. 2014, 126, 14070 – 14073.