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Catalytic Asymmetric Hydrogenation of 3-Ethoxycarbonyl Quinolin-2-ones and Coumarins

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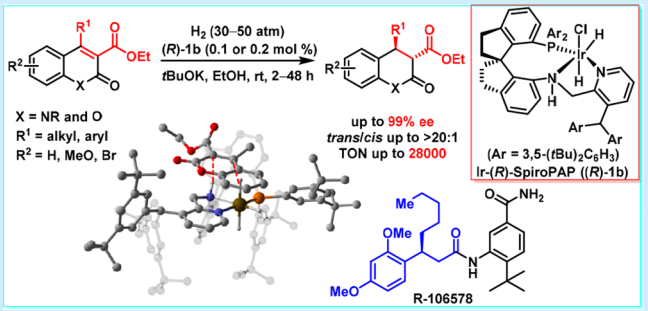
ABSTRACT: A protocol of iridium catalyzed asymmetric hydrogenation of 4-alkyl substituted 3-ethoxycarbonyl quinolin-2-ones and coumarins has been reported, providing a wide range of chiral dihydroquinolin-2-ones and dihydrocoumarins in high yields with excellent enantioselectivities (up to 99% ee) and high turnover numbers (up to 28 000). This efficient protocol was successfully applied for the synthesis of MPR3160 and the key chiral intermediate of R-106578.



Chiral dihydroquinolin-2-ones and dihydrocoumarins are common structural motifs in natural products and pharmaceuticals.[1] Typical and significant examples of these chiral heterocyclic molecules are those having alkyl or aryl substituents at the C4-position[2] (Figure 1). In addition, these

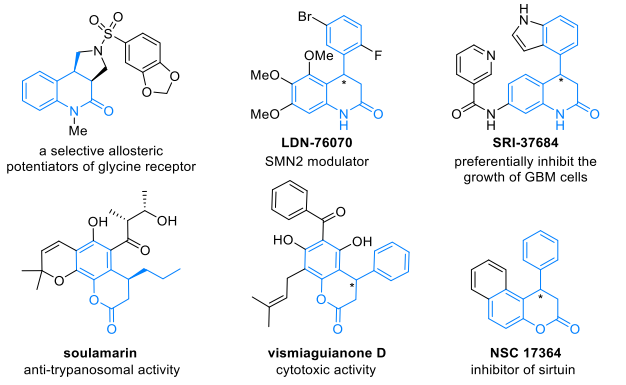
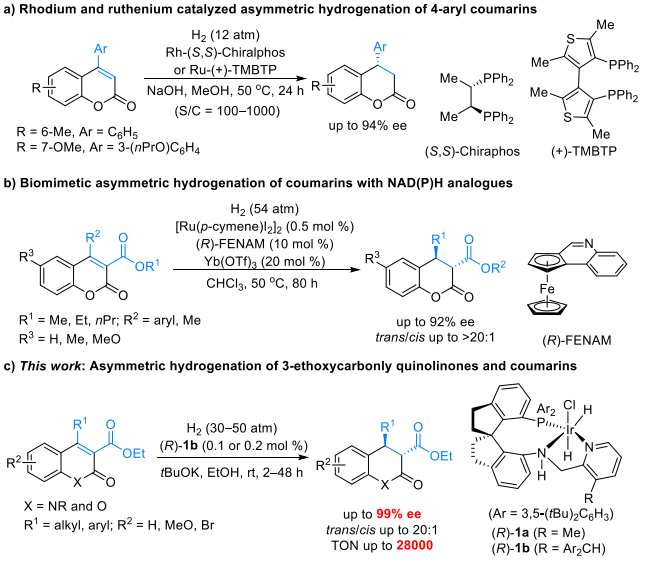


Figure 1. Selected pharmaceuticals and natural products containing chiral dihydroquinolin-2-one and dihydrocoumarin structures.

heterocyclic molecules are also important chiral building blocks for the synthesis of pharmaceuticals and bioactive natural products.[3] As a consequence, the development of efficient methods for the enantioselective syntheses of such heterocyclic molecules has received much attention.[4] Among them, the asymmetric hydrogenation of coumarins catalyzed by rhodium and ruthenium complexes of chiral diphosphine ligands[5] (Scheme 1a) and a biomimetic NAD(P)H analogue (*R*)-FENAM in combination with achiral ruthenium catalyst[6] (Scheme 1b) has been demonstrated to be one of the most efficient ways of accomplishing the goal. However, the

Scheme 1. Asymmetric Hydrogenation of Quinolones and Coumarins



substrates are limited to 4-aryl substituted coumarins and no report has been published for the asymmetric hydrogenation of

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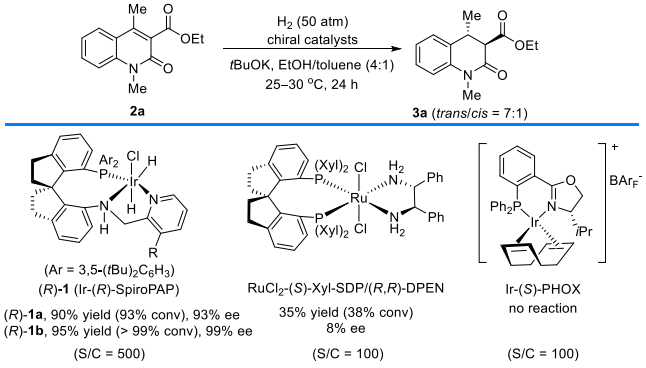
quinolin-2-ones for the synthesis of chiral dihydroquinolin-2-ones.[7]

We have recently found that chiral iridium complexes of SpiroPAP ligands are extremely efficient catalysts for the asymmetric hydrogenation of ketones[8] and esters[9] and were also highly efficient for the asymmetric hydrogenation of electron-deficient tetrasubstituted olefins.[10] These interesting results encouraged us to investigate the possibility of applying chiral spiro iridium catalysts into the asymmetric hydrogenation of quinolin-2-ones and coumarins. The results showed that chiral spiro iridium catalysts (*R*)-**1** could be highly efficient for the hydrogenation of 4-substituted 3-ethoxycarbonyl quinolin-2-ones and coumarins, providing the corresponding chiral dihydroquinolin-2-ones and dihydrocoumarins in high yields with excellent enantioselectivities (Scheme 1c). Herein we report the results of asymmetric hydrogenation of 4-substituted 3-ethoxycarbonyl quinolin-2-ones and coumarins with Ir-SpiroPAP catalysts.

We initially selected 4-methyl 3-ethoxycarbonyl quinolin-2-one **2a** as a standard substrate to evaluate several catalysts in the presence of *t*BuOK as base and toluene as a cosolvent[11] in EtOH under 50 atm of H_2 at room temperature (Scheme 2).

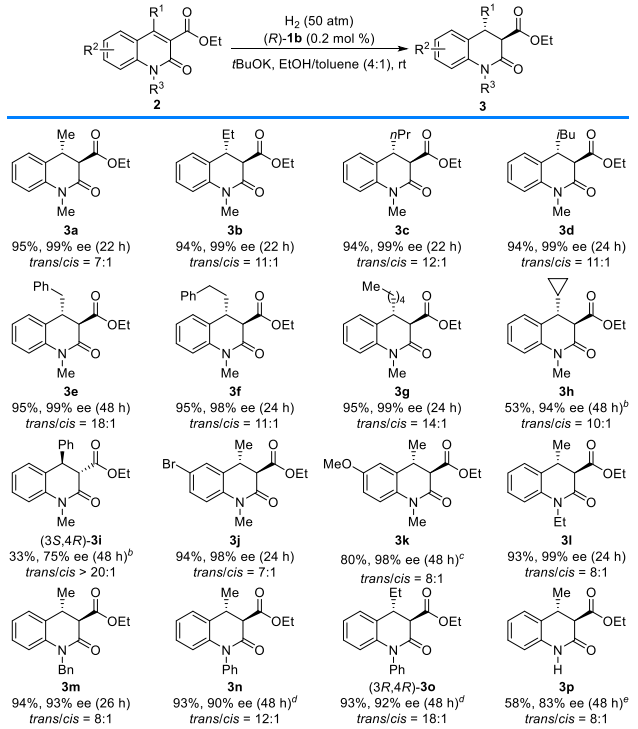
Scheme 2. Evaluation of Chiral Catalysts for the Asymmetric Hydrogenation of 2a



We found that the hydrogenation could be completed within 24 h with (*R*)-**1b** as a catalyst, and the corresponding hydrogenated product *trans*-**3a** was obtained in 95% yield with 99% ee in a ratio of 7:1. Comparable results were also achieved with (*R*)-**1a** as a catalyst (90% yield and 93% ee), but with a low yield and poor enantioselectivity (35% yield with 8% ee), and no hydrogenation was observed with chiral ruthenium catalyst $RuCl_2$-(*S*)-Xyl-SDP/(*R*,*R*)-DPEN[12] and chiral iridium catalyst Ir-(*S*)-PHOX,[13] respectively. It is worth noting that the hydrogenation products were dominated by thermodynamically preferred *trans*-**3a** and the ratio of *trans*- to *cis*-isomer was determined by the thermodynamic stability constant between the isomers because the new generated stereocenter at C3 could be easily epimerized under a strong base condition. Thus, we selected (*R*)-**1b** as the choice of catalyst and tested a series of 3-ethoxycarbonyl quinolin-2-ones **2** under the same reaction conditions.

As shown in Scheme 3, the 3-ethoxycarbonyl quinolin-2-ones **2a**–**g** with 4-alkyl substituents could be smoothly hydrogenated to the corresponding chiral dihydroquinolin-2-ones **3a**–**g** in high yields (94–95%) with excellent enantioselectivities (98–99% ee). By changing these less hindered alkyl substituents into relatively bulky cyclopropyl (**2h**) and phenyl (**2i**) groups, the reaction rates became very

Scheme 3. Asymmetric Hydrogenation of 3-Ethoxycarbonyl Quinolinones 2 with Catalyst (*R*)-1b[a]



[a]Reaction conditions: 1.0 mmol scale, (*R*)-**1b**/*t*BuOK/**2** = 1:400:500, EtOH (2.0 mL), toluene (0.5 mL), room temperature (25–30 °C), 50 atm of H_2; isolated yields. The *trans*/*cis* ratio was determined from the crude ^{1}H NMR spectra, and the ee value was determined by chiral HPLC analysis. [b]0.2 mol % (*R*)-**1a**. [c]0.4 mol % (*R*)-**1b**, 50 °C. [d]0.4 mol % (*R*)-**1a**. [e]0.4 mol % (*R*)-**1a**, 50 °C.

sluggish and less than 10% conversions were observed with (*R*)-**1b**. Fortunately, by replacing (*R*)-**1b** with (*R*)-**1a** as the catalyst and extending the reaction time to 48 h, a 53% yield with 94% ee and 33% yield with 75% ee were observed for the hydrogenation of **2h** and **2i**, respectively. Installing an electron-withdrawing (**2j**) or electron-donating group (**2k**) has little influence on the enantioselectivity (both 98% ee) while the former achieved higher yields (**3j**–**k**). The substituent at the nitrogen atom also has a noticeable effect on the reaction rate and the enantioselectivity. When a methyl group at the nitrogen atom of **2a** (R = Me) was replaced by another alkyl group such as ethyl (**2l**) and benzyl (**2m**), comparable results were observed. However, when it was replaced by a phenyl group such as **2n** and **2o**, very low conversions (<10%) were observed with catalyst (*R*)-**1b**. Likewise, higher yields with high enantioselectivities were obtained for the hydrogenation of **2n** (93% yield, 90%ee) and **2o** (93% yield, 92% ee) with (*R*)-**1a**, but a longer reaction time and higher catalyst loading were required. The substrate **2p** (R = H) with no substituent at the nitrogen atom could also be hydrogenated with (*R*)-**1b** at a higher reaction temperature (50 °C), providing **3p** in 58% yield with 83% ee.

These exciting results encouraged us to further explore the asymmetric hydrogenation of 4-alkyl substituted 3-ethoxycarbonyl coumarins **4** (Scheme 4). Although high enantioselectivity has been achieved by Zhou's[6] biomimetic asymmetric reduction with NAD(P)H analogues based on chiral ferrocene with hydrogen gas as the terminal reductant (Scheme 1b), low

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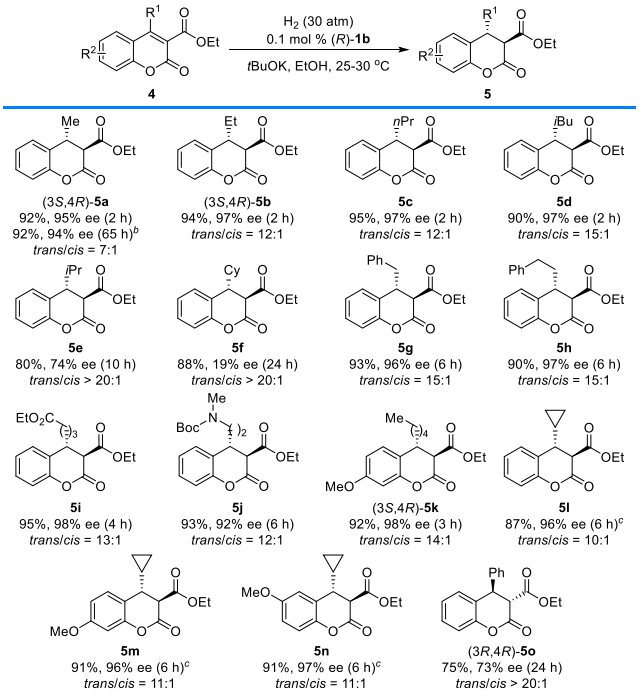
Scheme 4. Asymmetric Hydrogenation of Chromen-2-ones 4 with Catalyst (*R*)-1m[a]



[a]Reaction conditions: 1.0 mmol scale, (*R*)-**1b**/*t*BuOK/**4** = 1:400:1000, EtOH (2.0 mL), room temperature (25−30 °C), 30 atm of H_2; Isolated yield; The *trans*/*cis* ratio was determined from the crude ^{1}H NMR spectra, and the ee value was determined by chiral HPLC analysis. [b]0.0033 mol % (*R*)-**1b**, 60 atm of H_2 (initial). [c]0.2 mol % (*R*)-**1b**.

yield and moderate enantioselectivity (69% ee) were observed for the hydrogenation of 4-methyl 3-ethoxycarbonyl coumarin (**4a**). Under the similar conditions with (*R*)-**1b** as the catalyst (0.1 mol % (*R*)-**1b** and 30 atm of H_2), we found that the asymmetric hydrogenation of 4-alkyl substituted 3-ethoxycarbonyl chromen-2-ones **4a**−**k** were completed within 2 h and afforded the corresponding 3,4-dihydrocoumarins **5a**−**k** in high yields (up to 95%) and excellent enantioselectivities (up to 98% ee). The coumarin substrates bearing a less sterically hindered 4-alkyl group, such as methyl (**4a**), ethyl (**4b**), and *n*-propyl (**4c**), gave a higher yield and enantioselectivity. Lower yields and enantioselectivities were observed for the substrates with a relatively bulkier 4-alkyl group, such as *i*Pr (**4e**) and Cy (**4f**). The ester (**4i**) and Boc-amino (**4j**) group in the substrates were compatible in the reaction. The chromen-2-ones **4l**−**n** with a cyclopropyl group also afforded reduction products **5l**−**n** in high yields and excellent enantioselectivities (96−97% ee), providing an efficient and potential approach to chiral pharmaceuticals with a cyclopropyl substituted benzylic stereocenter.[14] The substrate with a 4-phenyl group (**4o**) could also be hydrogenated by catalyst (*R*)-**1b**, but with a lower enantioselectivity (73% ee). Furthermore, a catalyst loading experiment showed that the hydrogenation of **4a** could be performed at a very low catalyst loading (0.0033 mol % (*R*)-**1b**, S/C = 30 000) at 60 atm of H_2 pressure, providing (3*S*,4*R*)-**5a** in 92% yield (TON = 28 000) and 94% ee.

We selected coumarin **4a** as a model substrate and performed DFT calculations to understand the origins of the stereochemistry of reaction. The substrate **4a** was through a six-membered-ring transition state (outer-sphere mechanism[15]) to approach the catalyst (*R*)-**1b**.[10b] To minimize the steric repulsion of the bulky group at the 3-position of the pyridine ring and the rigid spiro backbone of the catalyst, the substrate **4a** tends to approach the catalyst in the direction of the ester side close to the rigid spiro backbone (Figure 2).

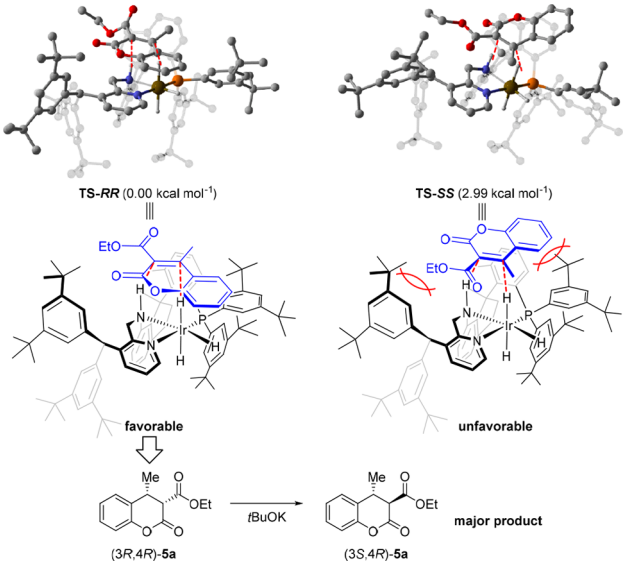


Figure 2. Models of stereochemistry control for asymmetric hydrogenations of **4a**.

Thus, TS-*RR* was favorable for **4a**, leading to the formation of (3*R*,4*R*)-**5a**. Since *cis*-product (3*R*,4*R*)-**5a** was prone to epimerize to thermodynamically more stable *trans*-isomer (3*S*,4*R*)-**5a** under basic conditions, a mixture of products dominated by *trans*-isomer (3*S*,4*R*)-**5a** was finally observed. The calculation result (98% ee) is in good agreement with the experimental result (95% ee). Furthermore, based on these transition state models we can also explain why low reactivity and moderate enantioselectivity with "opposite" configuration were observed for the hydrogenation of 4-aryl substituted substrates such as **2i** and **4o** with (*R*)-**1b**. To avoid the larger steric hindrance between the aryl group and the rigid spiro backbone of the catalyst (*R*)-**1b**, TS-*SS*, instead of TS-*RR*, became favorable, which led to the formation of hydrogenated products such as **3i** and **5o** with (3*S*,4*R*) and (3*R*,4*R*) configurations, respectively.

To exemplify the utility of these efficient asymmetric hydrogenations, we performed the enantioselective synthesis of a cholesterol acyltransferase (ACAT) inhibitor R-106578[16] and a selected 5-HT_{1A} receptor antagonist MPR3160[17] (Scheme 5). The asymmetric hydrogenation of **4k** (6.4 g, 20 mmol) with (*S*)-**1b** (0.005 mol %, S/C = 20 000) under 60 atm of H_2 at room temperature for 60 h provided (3*R*,4*S*)-**5k** in 92% yield with 98% ee. The decarboxylation of (3*R*,4*S*)-**5k**, followed by a hydrolytic opening of the lactone ring and a subsequent methylation of the phenol, afforded the acid (*S*)-**7**, a key intermediate for the synthesis of R-106578, in 68% yield over two steps. The enantioselective synthesis of MPR3160 was initiated by the methylation of (3*R*,4*R*)-**3o** with methyl iodide followed by hydrolysis in one pot to deliver an acid (3*S*,4*S*)-**8** in 91% yield. The acid (3*S*,4*S*)-**8** was then converted into MPR3160 via a Curtius rearrangement followed by the reduction with borane. It is noteworthy that the absolute configuration of **3o** and **8** were assigned as (3*R*,4*R*) and

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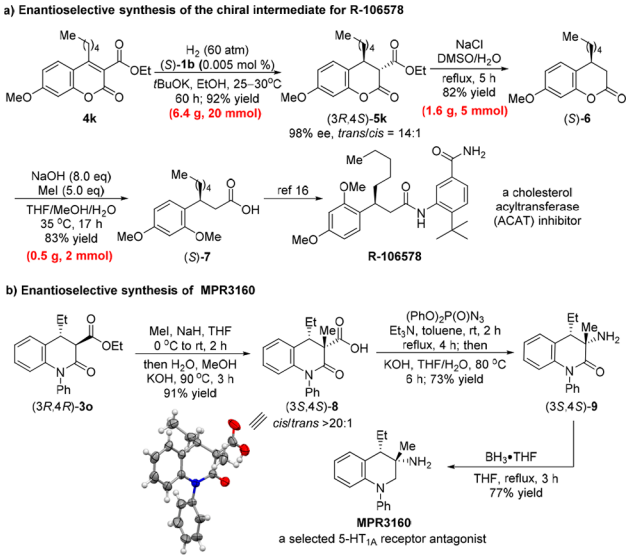
Scheme 5. Enantioselective Synthesis of R-106578 and MPR3160



(3*S*,4*S*), respectively, by X-ray diffraction analysis of the crystal structure of acid **8**.

In conclusion, we have developed an efficient catalytic asymmetric hydrogenation of 3-ethoxycarbonyl quinolin-2-ones and coumarins. With chiral spiro iridium catalyst (*R*)-**1b**, a wide range of 4-alkyl substituted 3-ethoxycarbonyl quinolin-2-ones and coumarins were hydrogenated to chiral dihydroquinolin-2-ones and dihydrocoumarins in high yields with excellent enantioselectivities (up to 99% ee) and high turnover numbers (up to 28 000). This protocol was successfully applied for the enantioselective syntheses of MPR3160 and the key chiral intermediate of R-106578.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00993.

Synthetic procedures, characterization, and additional data (PDF)

Accession Codes

CCDC 2060089 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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