Tetrahedron 72 (2016) 1375–1380

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

First catalytic asymmetric hydrogenation of quinoxaline-2-carboxylates

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ARTICLE INFO

Article history:
Received 12 December 2015
Received in revised form 15 January 2016
Accepted 18 January 2016
Available online 20 January 2016

Keywords:
Quinoxaline-2-carboxylates
Asymmetric hydrogenation
Iridium
Tetrahydroquinoxaline-2-carboxylates
Automated development

ABSTRACT

For the first time, the asymmetric hydrogenation of quinoxaline-2-carboxylates was performed successfully. The best catalysts are based on iridium complexes modified by chiral phosphorous ligands. Accelerated examination of ligands and catalysts has been undertaken by using a Chemspeed workstation, which enables carrying out, in parallel, eight independent catalytic reactions at the laboratory scale. Tetrahydroquinoxaline-2-carboxylates could be obtained with high yields and up to 74% ee.

1. Introduction

The asymmetric hydrogenation of heteroaromatic compounds is a very important transformation in organic chemistry owing to the fact that it offers a straightforward, highly versatile and environmentally friendly process to obtain optically pure heterocyclic building blocks.[1] The latter are widespread in bioactive compounds, which can be either natural or artificial. Heterocyclic substrates such as, for example, quinolines,[2] isoquinolines,[3] quinoxalines,[4] pyrroles,[5] indoles,[6] imidazoles and oxazoles,[7] benzoxazines,[4p–r] pyrazines,[8] furanes,[9] thiophenes[10] and benzothiophenes,[11] pyridines,[12] and indolizines[13] have been successfully hydrogenated recently with high conversions and enantioselectivities. Nonetheless, because of the substrates specificity, a suitable catalyst needed to be developed each time with respect to the structure of the heterocyclic substrate skeleton and its substituents. Generally, the development of asymmetric catalysts is based on experience, intuition, design, and trial and error. The entire optimization process can be quite time intensive as a consequence of the large number of experimental parameters to be screened. With a library of ligands or catalysts, a high-throughput screening represents a convenient way to find the optimum catalyst for a selected transformation or substrate.[14]

Various transition metal catalysts as well as organocatalysts have been developed for the enantioselective hydrogenation of quinoxalines,[4] as tetrahydroquinoxalines are of great biological interest.[15] To date, only 2- and 2,3-alkyl- or aryl-substituted quinoxalines have been successfully hydrogenated.[4] No report describes the enantioselective hydrogenation of acid derivatives of 2-functionalized quinoxalines. Nevertheless, it must be emphasized that Minnaard, Feringa, de Vries and co-workers reported in 2009 an unfruitful attempt to hydrogenate methyl quinoxaline-2-carboxylate.[4q] It appears thus that the enantioselective hydrogenation of this substrate is not trivial.

We have a long standing interest for the application of asymmetric hydrogenation in the synthesis of enantioenriched building blocks,[16] and, in particular, non-proteinogenic amino-acids. Our last contribution to this domain concerned the enantioselective hydrogenation of 2-functionalized quinolines.[2f] Rationally, we thought to investigate the access to enantioenriched 1,2,3,4-tetrahydroquinoxaline-2-carboxylates, as the corresponding α-amino acid has not been much investigated so far. Indeed, besides having the potential to be a building block of interest, it can also

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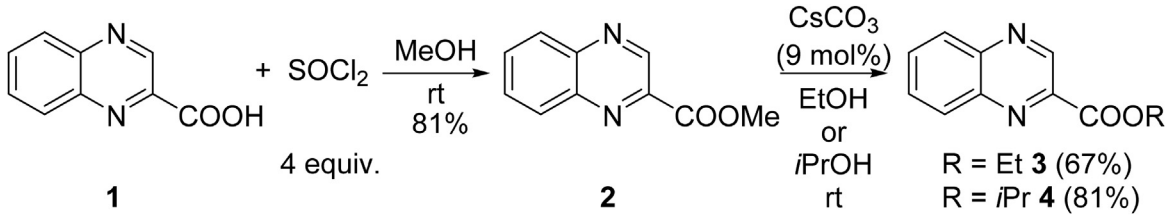
http://dx.doi.org/10.1016/j.tet.2016.01.033
0040-4020/

provide a useful scaffold in the area of cyclic amino acids, which constitute an important class of compounds for drug discovery and biomedical research. Cyclic amino acids adopt unique amide bond conformations that influence the three dimensional structure of peptides and proteins.[17] Thus, a synthetic approach to 1,2,3,4-tetrahydroquinoxaline-2-carboxylic acids by catalytic asymmetric hydrogenation would be highly useful. Herein, we report on our successful efforts to enantioselectively hydrogenate quinoxaline-2-carboxylates.

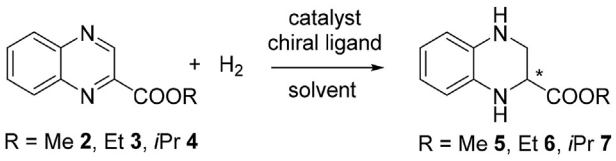
2. Results and discussion

The methyl ester substrate **2** was synthesized by esterification of the commercial quinoxaline-2-carboxylic acid **1** in the presence of thionyl chloride in methanol. The ethyl **3** and *iso*propyl **4** esters were obtained, in separate experiments, by transesterification of methyl quinoxaline-2-carboxylate **2** in ethanol or *iso*propanol, respectively, in the presence of a catalytic amount of cesium carbonate (Scheme 1).



Scheme 1. Synthesis of substrates **2**–**4**.

In order to identify a promising catalytic system for further optimization, we performed a first screening of hydrogenation reactions of **2** based on eight parallel experiments (Scheme 2). Details related to the screening platform are given in the experimental section. A series of catalysts was either prepared in situ from iridium (**C1**–**C4**) and ruthenium (**C5**) precursors or obtained from commercial preformed ruthenium complexes (**C6**–**C8**). For the first screening, we preferred also ligands that we applied successfully previously in the hydrogenation of quinoline carboxylates like Difluorphos **L5** and *P*-Phos **L9**[2f] (Fig. 1, Table 1). Iodine was used as an additive, as it proved being generally the best for activating iridium catalysts. Thus, catalytic assays were performed in the presence of the catalyst precursor (1% mol) in combination with diphosphines (when applicable) (1.1% mol) and iodine (10 mol %) only with iridium precursors in toluene under 80 bar H_2 at temperatures ranging from 10 to 60 °C.



Scheme 2. Hydrogenation of methyl **2**, ethyl **3** and isopropyl **4** quinoxaline carboxylates.

Catalysts obtained from iridium (I) complexes and diphosphines are the most promising ones. Indeed, when combining $[Ir(cod)Cl]_2$ **C1**, *P*-Phos ligand **L9** and iodine, the hydrogenation proceeded smoothly and gave the desired amino ester with an 84% yield and an enantiomeric excess of 48% (Entry 1, Table 1). As mentioned above, a catalytic system relying on the **C1** precursor, the monodentate phosphoramidite ligand PipPhos and piperidine chloride as an additive was not efficient for the hydrogenation of **2**.[4q] Notably, this reaction represents thus the first example of asymmetric hydrogenation of a quinoxaline-2-carboxylate. This shows that, despite the strong coordination potential of both the substrate and product, the selective hydrogenation of the heterocycle is not hindered under the catalytic conditions developed in the present work. We reproduced this single experiment in a laboratory setup and applied exactly the same experimental conditions and were delighted to obtain very close results (82% yield, 46% ee vs 84% yield, 48% ee in the automated system). The catalyst obtained from **C2**, which is an Ir (0) precursor and ligand **L9** in the presence of iodine, was less efficient both in terms of conversion and enantioselectivity leading to 34% yield and 6% ee (Entry 2). The catalyst obtained from the iridium (I) precursor **C4** bearing cyclooctene ligands was not leading to an efficient catalytic system (Entry 3). This trend suggests that the type of olefinic ligands present in the iridium (I) precursor is important for the in situ preparation of the active species.

From this initial study, we can conclude that Cp*Ir(III) based precursors as well ruthenium based catalysts and the conditions applied are not suitable for the hydrogenation of **2** (Entries 3 and 5–8) even though ruthenium catalysts have been found efficient for the hydrogenation of alkyl-2 quinoxalines.[18]

The next series of experiments showed that the hydrogenation is strongly solvent-dependent (Fig. 2).

If the use of dichloromethane provided a slightly beneficial effect on the hydrogenation activity (95% vs 84% yield), a dramatic effect was noticed on enantioselectivity, which was much lower when compared to that obtained when using toluene (25% ee vs 48% ee). Tetrahydrofuran and *iso*propanol were not adequate solvents for this reaction with lower yields together with low enantioselectivity. Thus, toluene was identified as the best reaction medium regarding enantioselectivity.

We further observed that a higher pressure was beneficial to the conversion, whereas a reaction temperature of 10 °C allowed the highest enantioselectivity (Fig. 3). The best result was thus obtained in toluene at 10 °C and under 80 bar of H_2 (84% conv., 84% yield into **5** and 48% ee).

From these sets of experiments, we could thus define suitable catalytic conditions that were subsequently used to screen a set of chiral ligands in order to evaluate their ability for improving the hydrogenation enantioselectivity (Fig. 4).

Under optimized conditions, a variety of chiral phosphorous ligands comprising atropisomeric diphosphines based on biphenyl **L1**–**L8** and **L10**–**L14** and bipyridyl **L9** scaffolds, the diphosphines CatASium®T3 **L15**, spirodiphosphine **L16**, monophosphite **L17**, the phosphoramidites **L18**–**L20**, and the ferrocenic diphosphines **L21**–**L27** were applied in catalytic assays. The results from the ligands evaluation during hydrogenation of substrate **2** are presented in Fig. 4. No general trend related either to the conversion or to the enantioselectivity could be drawn from such results.

As shown in Fig. 4, conversions over 80% were obtained in the presence of a few diphosphorous ligands, i.e., atropisomeric