Tetrahedron Letters 56 (2015) 192–194

Contents lists available at ScienceDirect

Tetrahedron Letters

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

# Asymmetric transfer hydrogenation of α-azido acrylates

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ARTICLE INFO

*Article history:*
Received 27 July 2014
Revised 4 November 2014
Accepted 14 November 2014
Available online 21 November 2014

*Keywords:*
Asymmetric transfer hydrogenation
α-Hydroxy esters
Azides
Ru-TsDPEN catalyst
Lactates

ABSTRACT

The asymmetric transfer hydrogenation of α-azido acrylates has been explored, a range of α-hydroxy esters are produced with good enantioselectivities (80–90% ee). The reaction was conducted in the wet $HCO_2H/NEt_3$ with Ru-TsDPEN **A**.



Enantio-enriched α-hydroxy carboxylic acids and their derivatives are very important precursors for the preparation of a variety of significant compounds.[1] The preparation of them has attracted broad interest from chemists.[2] The most general method toward them is the catalytic asymmetric reduction of α-keto carboxylic acids or α-keto esters. Following our continuous research on the reaction of alkenyl azides,[3,4] herein we report an efficient preparation of chiral α-hydroxy esters through the asymmetric transfer hydrogenation of α-azido acrylates.

The reduction of azide to amine[5] and the conversion of alkene to alkane[6] could be realized under the hydrogenation conditions. Therefore, part hydrogenation of an alkenyl azide would afford two different types of products, known as alkyl azide and enamine. The alkyl azide would be produced if the hydrogenation of alkene was preferred over the azido group, and it could be further converted to an amine under the hydrogenation conditions. On the contrary, enamine would be afforded if reduction of the azido group was prior to the alkene. The enamine could be easily hydrolyzed to a ketone, which would be further converted to an alcohol under the reducing conditions.[6] So if the chiral reductant could control the order of hydrogenation with good enantioselectivity, the dominant product would be either the enantio-enriched amine or the chiral alcohol.

The α-azido acrylates could be easily prepared from the condensation of aldehydes with the α-azido acetate according to the reported procedure.[7] We decided to explore the asymmetric transfer hydrogenation of the α-azido acrylates with the selected commercially available Ru-TsDPEN catalysts **A**–**E** (Fig. 1).

The α-azido cinnamate **1a** was selected for the initial investigation. To our delight, the phenyl lactate **2a** was obtained with all the Ru-TsDPEN catalysts **A**–**E** in the $HCO_2H/NEt_3$ azeotrope. If a small amount of water was added, the conversion could be accelerated. Then all the experiments were conducted with the wet $HCO_2H/NEt_3$ (Table 1). Among the catalysts (3 mol %) examined here, Ru-TsDPEN (*S*,*S*)-**A** gave the best result, and the phenyl lactate **2a** was obtained in 84% yield with 88% enantioselectivity. The transfer hydrogenation of **1a** with catalyst (*R*,*R*)-**E** produced ester **2a** with the same enantioselectivity, but the yield was slightly lower. Further optimization with different ratio of $HCO_2H/NEt_3$ using (*R*,*R*)-**E** failed to give better result. Transfer hydrogenation of **1a** at room temperature with (*S*,*S*)-**A** resulted in longer reaction time and lower conversion. Fortunately, 0.5 mol % of (*S*,*S*)-**A** catalyzed the reaction well, and the similar enantioselectivity (90% ee) and yield (84%) were observed. The absolute stereochemistry of **2a** was assigned as the *S* configuration by comparison of the rotation data ($[\alpha]_D$ −13.7) with that of the previous reports ($[\alpha]_D$ +15.5 with the *R*-enantiomer).[8] The catalytic activities of (*S*,*S*)-**A** and (*R*,*R*)-**E** are superior to others. This is most likely due to the phenyl side-arm of the diamine ligand, which stabilizes the active Ru species so that the longevity of the catalyst gets improved.

We next explored the scope of the α-azido cinnamates with 0.5 mol % catalyst **A** (Table 2). The substrates with electron donating groups or electron withdrawing groups on the phenyl ring all proceeded the conversion smoothly, and gave the corresponding aryl lactates **2b**–**2h** in 81–90% yield with good enantioselectivities

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http://dx.doi.org/10.1016/j.tetlet.2014.11.072
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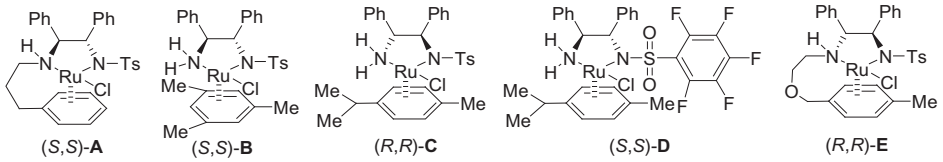
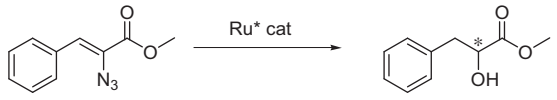


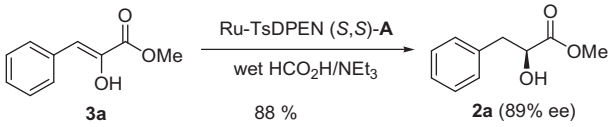

**Figure 1.** Ru-complex for asymmetric transfer hydrogenation of **1a**.

**Table 1**
Optimization of the asymmetric transfer hydrogenation of **1a**[a]




| Entry | Cat | Conditions | Time (h) | Yield[b] | ee[c] |
|---|---|---|---|---|---|
| 1 | (*S*,*S*)-**A** | $HCO_2H/NEt_3$ (5:2), 60 °C | 8 | 84 | 88 |
| 2 | (*S*,*S*)-**B** | $HCO_2H/NEt_3$ (5:2), 60 °C | 8 | 71 | 82 |
| 3 | (*R*,*R*)-**C** | $HCO_2H/NEt_3$ (5:2), 60 °C | 24 | 76 | −71[d] |
| 4 | (*S*,*S*)-**D** | $HCO_2H/NEt_3$ (5:2), 60 °C | 8 | 53 | 74 |
| 5 | (*R*,*R*)-**E** | $HCO_2H/NEt_3$ (5:2), 60 °C | 28 | 77 | −88[d] |
| 6 | (*R*,*R*)-**E** | $HCO_2H/NEt_3$ (7:2), 60 °C | 48 | 74 | −86[d] |
| 7 | (*R*,*R*)-**E** | $HCO_2H/NEt_3$ (2:1), 60 °C | 48 | 80 | −88[d] |
| 8 | (*R*,*R*)-**E** | $HCO_2H/NEt_3$ (5:2), rt | 72 | — | — |
| 9 | (*S*,*S*)-**A** | $HCO_2H/NEt_3$ (5:2), rt | 72 | 62 | 89 |
| 10 | (*S*,*S*)-**A** | $HCO_2H/NEt_3$ (5:2), 60 °C | 8 | 84 | 90[e] |

[a] Asymmetric hydrogenation of α-azido cinnamate **1a** (101 mg, 0.5 mmol) with Ru catalyst (3 mol %) in the presence of wet $HCO_2H/NEt_3$ under the conditions mentioned above.
[b] Isolated yield after acidic work up.
[c] Determined by chiral HPLC.
[d] Opposite enantioselectivity of the product was observed.
[e] Reaction with 0.5 mol % catalyst.



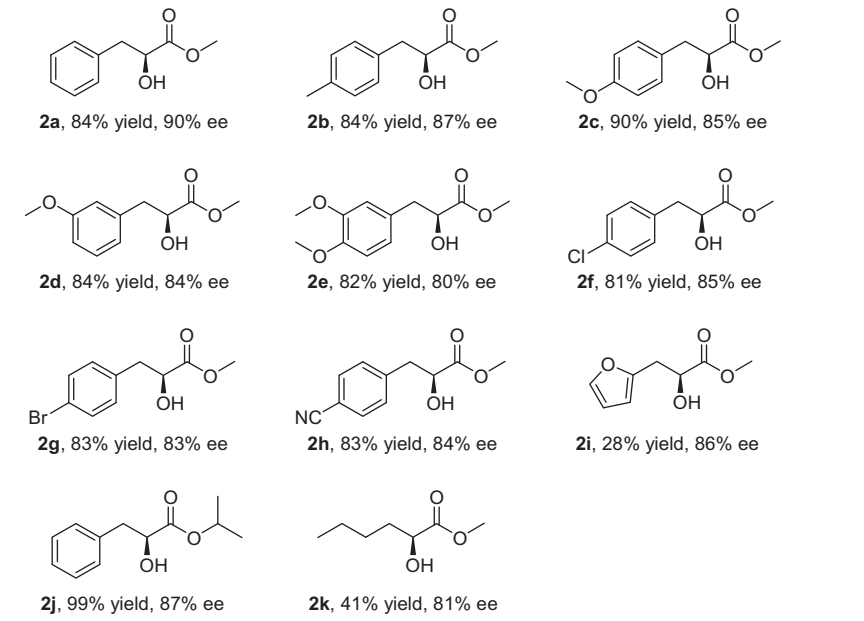

**Scheme 1.** Asymmetric transfer hydrogenation of α-keto ester **3a**.

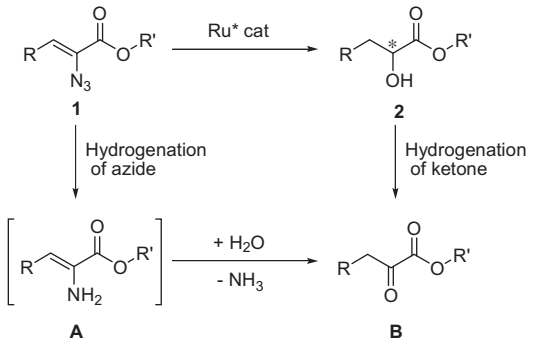
(80–87% ee). It should be noted here that the enantio-enriched α-hydroxy ester **2e** had been obtained from the lipase catalyzed resolution, and was used for the total synthesis of (+)-Pentamethylsalvianolic acid C.[9] Asymmetric hydrogenation of the fural substituted α-azido cinnamate **1i** faced a deep embarrassment, α-hydroxy ester **2i** was obtained in only 28% yield with a good control of enantioselectivity (86% ee). Enhancement of the load of catalyst from 0.5 mol % to 3 mol % did not improve the yield as well as the enantioselectivity. The isopropyl α-azido cinnamate was prepared, and subjected to the asymmetric transfer hydrogenation to see if the enantioselectivity could be improved. However no better result could be obtained with lactate **2j** (87% ee), while the yield was improved to 99%.

The asymmetric transfer hydrogenation of an α-azido β-alkyl-acrylate was also successful, but the α-hydroxy ester **2k** was obtained with very moderate yields (41%). The enantioselectivity (81% ee) of **2k** was determined with its benzoate by chiral HPLC. It should be noted that the *S* configuration of **2k** was also assigned by comparison of its rotation data ($[\alpha]_D$ −2.0, *c* 0.6 in EtOH) to that of the reported result.[10]

It should be noted that generally the corresponding α-keto ester could be found and isolated from the reaction mixture. Asymmetric hydrogenation of α-keto ester has been extensively explored, and generally the α-hydroxy ester could be obtained with good enantioselectivity and yields.[11] Herein, the asymmetric transfer hydrogenation of α-keto ester **3a** (with the stable enol form, 30.0 mg) with Ru-TsDPEN (*S*,*S*)-**A** under wet $HCO_2H/NEt_3$

**Table 2**
Scope of conversion






**Scheme 2.** A possible mechanism of asymmetric transfer hydrogenation of α-azido acrylate.

azeotrope has been studied (Scheme 1), and the phenyl lactate **2a** (26.7 mg) was obtained with 89% ee in 88% yield, which was comparable to that of α-azido cinnamate **1a** (90% ee, 84% yield). The preparation of an α,β-unsaturated ester (1,3-difunctional compound) by condensation of aldehyde and the α-azido acetate would be more convenient than that of α-keto ester (1,2-difunctional compound), though the former is more complex than the latter in view of their structures. To some extent, this conversion could be used as a supplement to the asymmetric transfer hydrogenation of α-keto ester.

From the above experiments and previous literatures, a proposed mechanism is outlined in Scheme 2. The conversion includes the following three stages: (1) Reduction of the azido group of the α-azido acrylate under the transfer hydrogenation conditions affords the unstable enamine intermediate **A**; (2) Hydrolysis of the enamine in the wet $HCO_2H/NEt_3$ azeotrope results in the α-keto ester **B**; (3) Asymmetric transfer hydrogenation of the α-keto ester with Ru-TsDPEN efficiently delivers the α-hydroxy ester **2** as the final product. The observed enantioselectivity of this process agreed with the asymmetric transfer hydrogenation of alkyl/alkyl ketones, which has been extensively discussed by Martin Wills and co-workers.[12]

In conclusion, the preparation of chiral α-hydroxy esters from the asymmetric transfer hydrogenation of α-azido acrylates have been demonstrated, and Ru-TsDPEN complex **A** is efficient to catalyze the conversion. The sequenced reaction is combined with azide reduction/enamine hydrolyzation/asymmetric transfer hydrogenation, and the enantioselectivities were good to excellent. Further research in our laboratory will focus on the conversion of α-azido acrylates to the enantio-enriched α-amino esters.

## Acknowledgment

This work was supported by the Ningxia Natural Science Foundation (NZ13046).

## Supplementary data

Supplementary data (experimental procedures and spectroscopic data and copies of NMR spectra and copies of HPLC spectra for all the products) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.072.

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