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Preparation of Enantioenriched γ-Substituted Lactones via Asymmetric Transfer Hydrogenation of β-Azidocyclopropane Carboxylates Using the Ru-TsDPEN Complex

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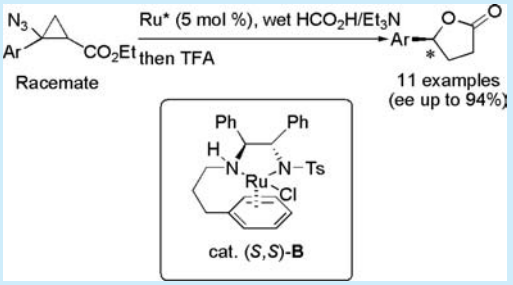
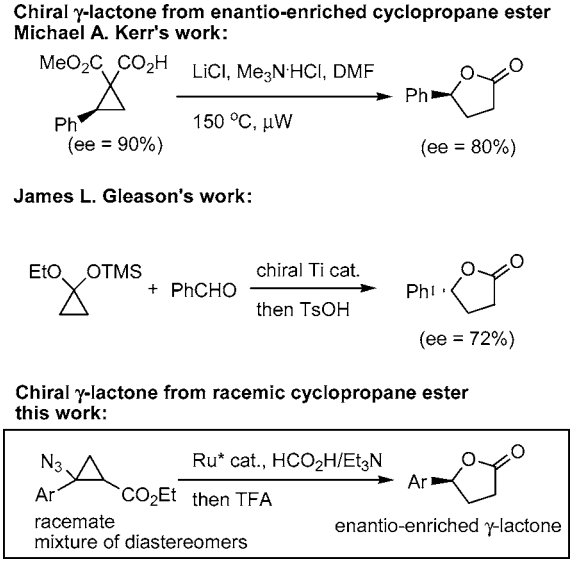
Supporting Information

ABSTRACT: The asymmetric transfer hydrogenation of racemic β-azidocyclopropane carboxylates has been explored. Ru-TsDPEN **B** is found to be a good catalyst for the formation of enantioenriched γ-lactones through a four-step sequence of azide reduction/cyclopropane ring cleavage/ketone transfer hydrogenation/lactonization, and the enantiomeric excess of the lactones was up to 94%.



The γ-lactone motif is found to be a very common unit in a variety of natural products,[1] and it is also a very useful building block in synthetic chemistry.[2] The preparation of these heterocycles has attracted broad interest from organic chemists,[3] and one method has incorporated the use of cyclopropanecarboxylates in ring reorganization.[4] However, the synthesis of such enantioenriched γ-lactones from cyclopropanes has been quite rare (Scheme 1). Kerr and co-workers have converted a range of cyclopropane hemimalonates into racemic γ-substituted lactones, and a slight erosion of enantiomeric excess was observed with one chiral substrate.[4a] Gleason and co-workers have reported the catalytic asymmetric homoaldol reaction of functionalized cyclopropane and aldehydes for the construction of enantioenriched γ-lactones; however, the enantioselectivity was modest (ee up to 72%).[4h,i] Following our research on the preparation and conversion of β-azidocyclopropane carboxylates,[5,6] herein we present the conversion of a range of racemic β-azidocyclopropane carboxylates to enantioenriched γ-substituted lactones through an asymmetric transfer hydrogenation process.

Scheme 1. Enantioenriched γ-Lactones from Cyclopropanes



In our research toward the preparation of conformationally restricted β-amino cyclopropane carboxylic acids (β-ACCs), we have developed an efficient method to address the *cis*-β-azidocyclopropane carboxylates with excellent control of relative and absolute configuration.[5] However, the Staudinger reduction of the enantioenriched β-azidocyclopropane carboxylates failed to afford the desired β-ACCs, and only the γ-oxo esters were produced in excellent yield.[6] It would be very easy to understand here that if the racemic cyclopropane carboxylates were used, the γ-oxo esters would also be efficiently produced. The asymmetric reduction of the γ-oxo esters has been reported with some chiral reagents via stoichiometric processes[7] or catalytic processes[8] with control of the stereochemistry. Thus, if a suitable chiral reductant was applied, further asymmetric reduction of the γ-oxo esters to enantioenriched γ-hydroxybutyrates might be possible.

According to the previous research and the above-mentioned conditions, the preparation of a chiral γ-lactone from a racemic β-azidocyclopropane carboxylate was designed through the

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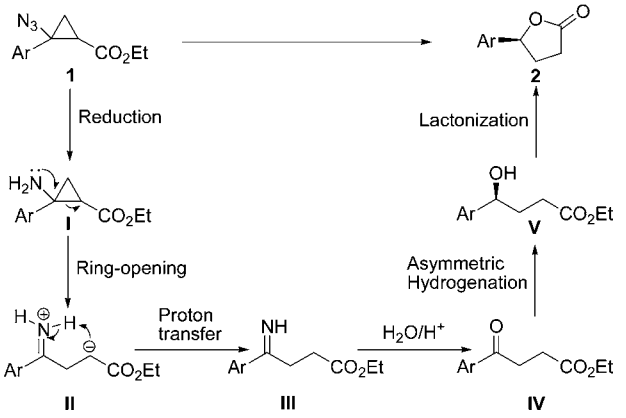
following stages: (1) the reduction of the azido group of the racemic cyclopropane carboxylate would afford the unstable donor−acceptor substituted cyclopropane carboxylate **I**; (2) ring opening of the cyclopropane carboxylate would afford the zwitterionic intermediate **II**,[9] and subsequent proton transfer would give imino ester **III**, which would be hydrolyzed to the γ-oxo ester **IV**; (3) asymmetric hydrogenation[10] of the γ-oxo ester would result in the chiral ethyl γ-hydroxybutyrate **V**; (4) lactonization under the acidic conditions would finally deliver the desired enantioenriched lactone **2** (Scheme 2).

Scheme 2. Designed Conversion of β-Azidocyclopropane Carboxylates to γ-Butyrolactones



For the designed process to be successful, the key issue is to find a good asymmetric reduction system, which must be comparable with the following requirements: (1) reduction of the azido group should be efficiently addressed; (2) the reactivity of the chiral reducing agent should be retained during the cyclopropane ring opening, as NH_3 released from the rearrangement could deactivate some metal catalysts; (3) the enantioselectivity of the hydrogenation must be well controlled. The designed reaction features two reduction processes, so at least 2 equiv of a chiral reductant must be used if a stoichiometric asymmetric reduction was employed. Thus, the catalytic asymmetric hydrogenation seemed to be more suitable. We decided to explore the following two types of commercially available Ru catalysts, Ru-BINAP complex **A** and Ru-TsDPEN catalysts **B**−**D** (Figure 1), which had been widely applied in the asymmetric hydrogenation or the related asymmetric transfer hydrogenation.

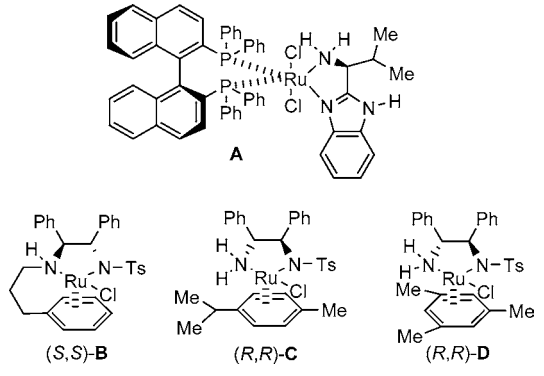
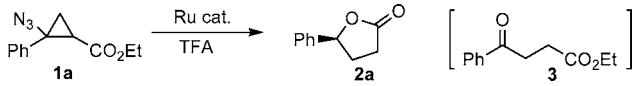


Figure 1. Ru-complex for asymmetric hydrogenation of the β-azidocyclopropane ester **1a**.

The racemic β-azidocyclopropane carboxylates could be easily prepared from the cyclopropanation of azido alkenes with ethyl diazoacetate in the presence of a Rh catalyst.[5] The investigation of the reaction was carried out with the β-azidocyclopropane carboxylate **1a** (Table 1). The initial study

Table 1. Asymmetric Hydrogenation of Ethyl β-Azidocyclopropane Carboxylate 1a[a]



entry	catalyst	conditions	time (h)	product (yield)	ee[e]
1	**A**	30 atm of H_2, MeOH, 25 °C	18	–	–
2	(*S*,*S*)-**B**	30 atm of H_2, MeOH, 60 °C	40	**3** (trace)[b]	–
3	(*R*,*R*)-**C**	30 atm of H_2, MeOH, 60 °C	40	**3** (trace)[b]	–
4	(*S*,*S*)-**B**	**HCO_2H/Et_3N (5:2), 60 °C**	**24**	**2 (69),[c] 2 (55)[d]**	**93, 94**
5	(*R*,*R*)-**C**	HCO_2H/Et_3N (5:2), 60 °C	24	**2** (62)[c]	−65[f]
6	(*R*,*R*)-**D**	HCO_2H/Et_3N (5:2), 60 °C	24	**2** (35)[c]	−88[f]

[a]Reaction of cyclopropane **1a** (40.0 mg, 0.17 mmol) with a Ru catalyst (0.085 mmol) under the conditions mentioned above. [b]Only trace γ-oxo ester **3** formed. [c]Isolated yield after acidic workup. [d]Transfer hydrogneation of 180.0 mg of cyclopropane **1a**. [e]Determined by chiral HPLC. [f]Opposite enantioselectivity of the product was observed.

of the asymmetric hydrogenation with the Ru-BINAP complex **A** was found to be invalid (Table 1, entry 1). It was thought that the Ru-BINAP complex **A** might be deactivated by the potential Staudinger reaction of the azido group with the BINAP ligand.[6] Thus, we switched to exploring the Ru(II) complexes containing TsDPEN ligands **B**−**D**. Hydrogenation of the β-azidocyclopropane carboxylate **1a** with Ru-TsDPEN catalysts **B** and **C** at 30 atm of H_2 and 60 °C for 40 h produced only trace γ-oxo ester **3**, and none of the desired ethyl γ-hydroxybutyrate or γ-lactone **2a** could be observed. To our delight, under the asymmetric transfer hydrogenation conditions with the wet HCO_2H/Et_3N azeotrope, a mixture of γ-hydroxybutyrates and γ-lactones was observed in the presence of all of the three Ru-TsDPEN catalysts. Treatment of the mixture with TFA afforded the lactone **2a** as the ultimate product. The best enantioselecitivity of the transformation was achieved with catalyst **B** containing the (*S*,*S*)-TsDPEN ligand. The absolute configuration of **2a** was assigned by comparison of the rotation data ($[\alpha]_D$ −22.3) with that of the previous reports.[11]

The lactone **2a** was obtained with excellent enantioselectivity from the transfer hydrogenation of the β-azidocyclopropane carboxylate **1a** with Ru-TsDPEN catalyst (*S*,*S*)-**B** followed by lactonization, but the yield was slightly reduced when the amount of **1a** was improved from 40.0 mg to 180.0 mg (Table 1, entry 4). For comparison, the transfer hydrogenation of γ-oxo ester **3** (32 mg) under similar conditions followed by TFA had been explored, and the resulting lactone **2a** was obtained in better yield (93%) but with slightly poor enantioselectivity (86% ee). The difference between the yields (69% vs 93%) of the two experiments could be easily understood, as the γ-oxo ester **3** was supposed to be the intermediate of the designed process. However, it was very interesting that the enantiose-

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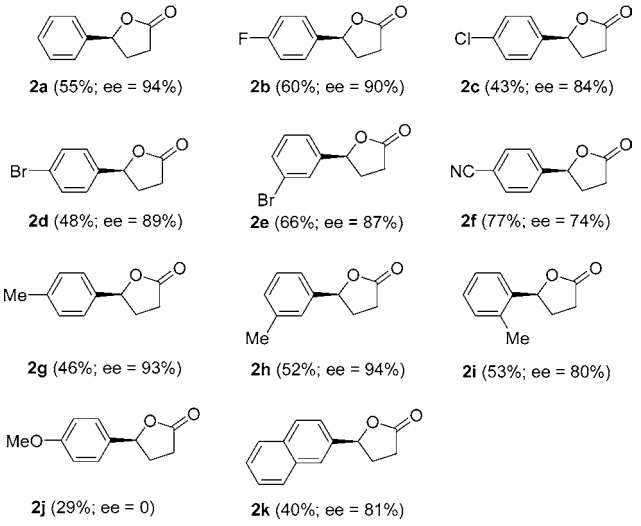
lectivity of hydrogenation of **1a** was better than that of the γ-oxo ester **3**. The γ-oxo ester seemed to be simpler than the β-azidocyclopropane carboxylate. But it should be noted here that the general method toward γ-oxo ester was the Stetter reaction of an aldehyde with an α,β-unsaturated compound, which was catalyzed by a highly toxic metal cyanide or a complex thiazolium salt.

With the above results, we next explored the scope of the substrates with Ru-TsDPEN catalyst (*S*,*S*)-**B** (Scheme 3). The

Scheme 3. Scope of Conversion[a]



[a]Reaction conditions: Asymmetric transfer hydrogenation of the β-azidocyclopropane carboxylate in the wet HCO_2H/Et_3N azeotrope with Ru-TsDPEN catalyst (*S*,*S*)-**B** (5 mol %) at 60 °C for 24 h. Then lactonization with TFA in CH_2Cl_2 after the removal of the HCO_2H/Et_3N azeotrope.

halogen-substituted phenyl substrates proceeded in the sequential reaction smoothly, producing lactones **2b**−**2e** in 43%−66% yield with good enantioselectivities (84−90% ee). Transfer hydrogenation of the 4-cyanophenyl β-azidocyclopropane carboxylate **1f** followed by lactonlization gave lactone **2f** in a better yield but with slightly decreased enantioselectivity. Attaching a methyl group at the para- and meta-position on the phenyl ring of the β-azidocyclopropane carboxylates resulted in slightly better enantioselectivity (**2g**, 93% ee; **2h**, 94% ee). However, introduction of a methoxyl group strongly decreased the conversion as well as the enantioselectivity. The naphthalene analogue was also examined, and the resulting lactone **2k** was obtained in 40% yield with good enantioselectivity (81% ee).

It should be noted here that the transformation proceeded through a multistep conversion, which is combined with the reduction of an azido group, cyclopropane ring rearrangement, asymmetric transfer hydrogenation of γ-oxo ester, and lactonization of ethyl γ-hydroxybutyrate. So even for the lactone **2k** with only a 40% yield, the average yield of the four steps reached up to 80%.

In conclusion, we have demonstrated that the Ru-TsDPEN complex **B** is a good catalyst for the asymmetric transfer hydrogenation of racemic β-azidocyclopropane carboxylate to enantioenriched γ-lactones. A four-step sequence of azide reduction/cyclopropane ring rearrangement/asymmetric transfer hydrogenation of γ-oxo ester/γ-lactonization produced 11 γ-lactones, and most lactones were obtained in good to excellent enantioselectivities.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data and copies of NMR spectra for all the β-azidocyclopropane carboxylates and γ-lactones. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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