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Synthesis of Chiral γ-Lactams via in Situ Elimination/Iridium-Catalyzed Asymmetric Hydrogenation of Racemic γ-Hydroxy γ-Lactams

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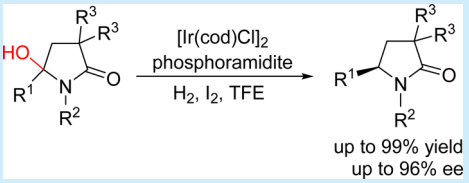
Supporting Information

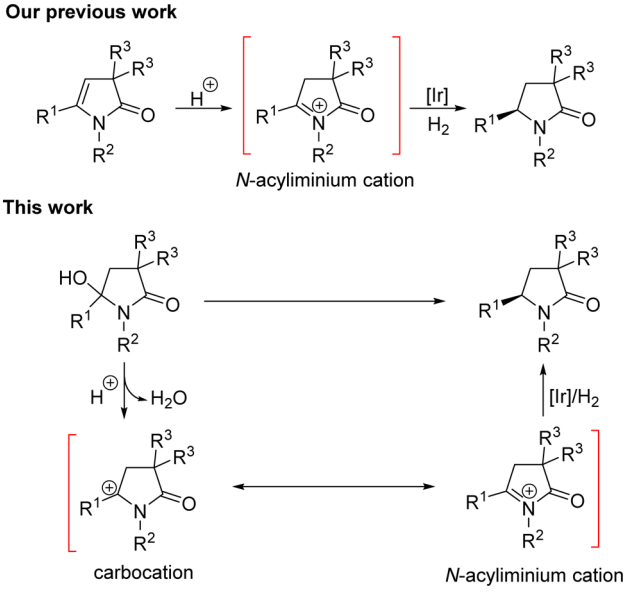
ABSTRACT: Chiral γ-lactams have been synthesized in excellent yields and enantioselectivities (up to 99% yield and 96% ee) from easily accessible racemic γ-hydroxy γ-lactams via an iridium-phosphoramidite catalyzed asymmetric hydrogenation. The reaction was designed based on insight into the reaction mechanism demonstrated in previous work and can be carried out at a reduced catalyst loading of 0.1 mol % on a gram scale. Several potential bioactive compounds can be synthesized from the reduced products. Mechanistic studies indicated that the reduced products were obtained via the hydrogenation of the *N*-acyliminium cations, generated from γ-hydroxy γ-lactams.



The chiral γ-lactam skeleton is an important structural motif,[1] and many impressive strategies for the synthesis of such structures have emerged,[2] such as Ru-catalyzed dehydrative intramolecular *N*-allylation,[3a] sequential allylic amidation and atom-transfer radical cyclization,[3b] Rh-catalyzed cycloisomerization[4a] and intramolecular C−H insertion reactions,[4b] Pd-catalyzed allylic alkylation,[5a] cyclopropane functionalizations,[5b] Au-catalyzed oxidative cyclization,[6] Cu-catalyzed C−H insertion reactions,[7] organocatalytic vinylic substitution,[8a] and conjugate addition.[8b] However, these methodologies usually require high catalyst loadings[3−8] and/or give the products with poor enantioselectivities.[7]

In recent years, we have focused on the development of transition-metal-catalyzed asymmetric hydrogenation reactions.[9,10] Very recently, we reported an iridium-catalyzed asymmetric hydrogenation of β,γ-unsaturated γ-lactams for the synthesis of chiral γ-lactams with excellent yields and enantioselectivities (Scheme 1).[10k] However, the synthetic route to β,γ-unsaturated γ-lactams is long, and β,γ-unsaturated γ-lactams with no substituents at the 3-position undergo facile isomerization to their corresponding α,β-unsaturated γ-lactams.[11] Mechanistic studies indicated that the reduced products were obtained via the hydrogenation of the *N*-acyliminium cations, generated from β,γ-unsaturated γ-lactams. These results prompted us to pursue more stable and accessible substrates for the synthesis of chiral γ-lactams. We speculated γ-hydroxy γ-lactams can be transformed to *N*-acyliminium cations via the following pathway: A carbocation is generated from the γ-hydroxy γ-lactam in the presence of H^+. Reduction of the other resonance form of the carbocation, *N*-acyliminium cation, gives the chiral γ-lactam product. An iridium-catalyzed asymmetric hydrogenation of *N*-acyliminium cations, generated from γ-hydroxy γ-lactams for the preparation of chiral γ-lactams (especially γ-lactams lacking substituents at the 3-position), was therefore designed (Scheme 1).

Scheme 1. Synthesis of Chiral γ-Lactams



γ-Hydroxy γ-lactams **1** can be easily synthesized from commercially available succinimide and Grignard reagents.[12] Compound **1a** was selected as a model substrate for the optimization of the reaction conditions (Table 1). First, we tested **1a** with our previously developed optimized reaction conditions for the iridium-catalyzed asymmetric hydrogenation

Received: March 3, 2017

DOI: 10.1021/acs.orglett.7b00651
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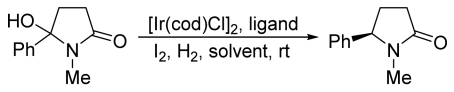
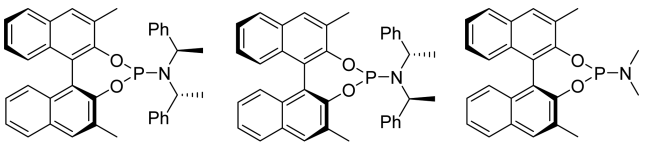
Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

entry	ligand	solvent	yield[b] (%)	ee[c] (%)
1[d]	**L1**	TFE/*t*AA	98	86 (*R*)
2[d,e]	**L1**	TFE/*t*AA	97	70 (*R*)
3	**L1**	TFE	98	90 (*R*)
4	**L1**	HFIP	73	51 (*R*)
5	**L1**	*t*AA	34	20 (*R*)
6	**L1**	DCM	97	17 (*S*)
7	**L1**	THF	99	40 (*R*)
8	**L1**	toluene	99	16 (*S*)
9	**L2**	TFE	98	77 (*R*)
10	**L3**	TFE	28	38 (*R*)
11[f]	**L1**	TFE	69	52 (*R*)
12[g]	**L1**	TFE	98	89 (*R*)

[a]Reaction was conducted on a 0.2 mmol scale in 2.0 mL of the solvent under 50 bar of H_2 at rt for 24 h, in the presence of $[Ir(cod)Cl]_2$ (0.5 mol %), ligand (2.2 mol %), and I_2 (10 mol %). [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]TFE/*t*AA (1.8 mL + 0.3 mL). [e]TFA (1.0 equiv) was added. [f]Under 40 bar of H_2. [g]Under 60 bar of H_2. cod = 1,5-cyclooctadiene. TFE = 2,2,2-trifluoroethanol. *t*AA = *tert*-amyl alcohol. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

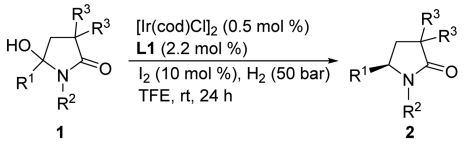


(*Sa*,*R*,*R*)-**L1** (*Sa*,*S*,*S*)-**L2** (*S*)-**L3**

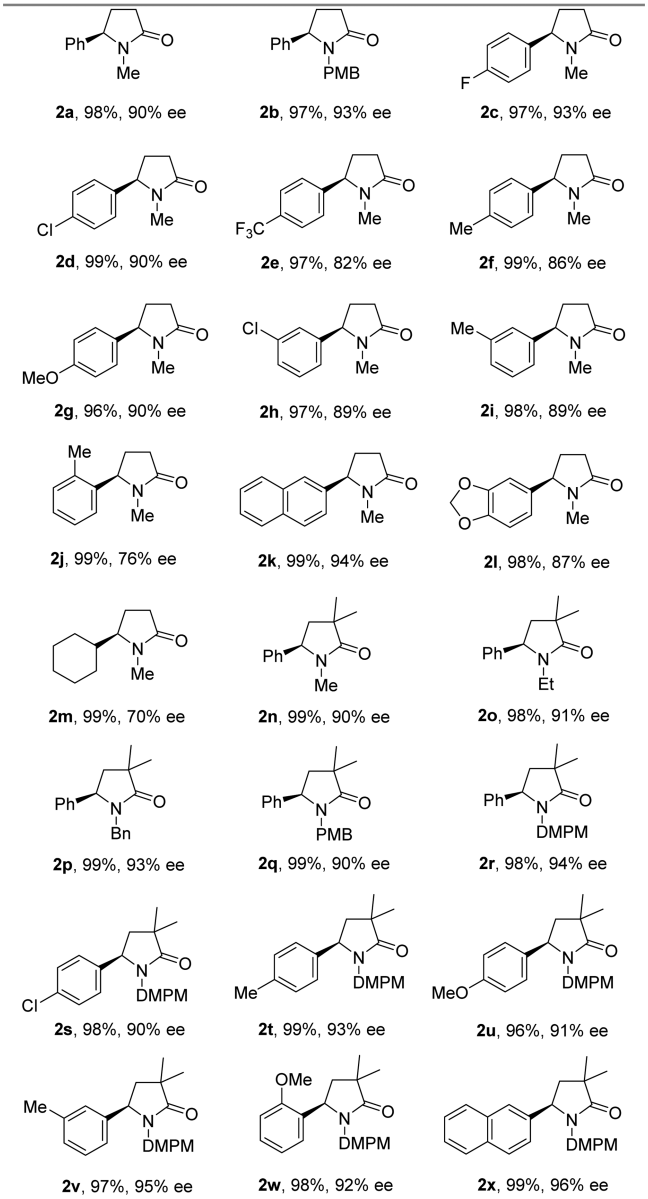
of *β*,*γ*-unsaturated *γ*-lactams.[10k] The reduced product **2a** was obtained with 86% ee and in 98% yield (entry 1). Notably, I_2 was necessary for the success of the reaction and has been used successfully in several iridium-catalyzed asymmetric hydrogenation reactions.[10k,13] When the reaction was carried out in the presence of TFA, the enantioselectivity of the hydrogenated product was reduced to 70% ee (entry 2). Next, the reaction solvent was examined and was found to have a significant influence on the reaction yield and enantioselectivity (entries 3−7). When using TFE as the reaction solvent, the reduced product was obtained with 90% ee and in 98% yield. A moderate ee was obtained when using HFIP as the reaction solvent (entry 4); however, the desired product was obtained with poor enantioselectivity and yield when *tert*-amyl alcohol was used as the reaction solvent (entry 5). The reactions proceeded well in aprotic solvents giving the reduced products in excellent yields but with low enantioselectivities (entries 6−8). Other binaphthyl phosphoramidite ligands **L2**−**L3** were also tested; both were inferior to **L1** (entries 9 and 10 vs 3). Finally, the effect of hydrogen pressure on the reaction was investigated. The desired product was obtained with 52% ee and in 69% yield when the reaction was conducted at 40 bar of hydrogen pressure (entry 11). Increasing the pressure of hydrogen to 60 bar gave the desired product with 89% ee and in 98% yield (entry 12).

With the optimized reaction conditions in hand (Table 1, entry 3), a variety of *γ*-hydroxy *γ*-lactams were tested (Scheme 2). The reduction of **1** bearing a *N*-PMB (4-methoxybenzyl) group gave its corresponding products with better enantioselectivity than the substrate bearing a *N*-Me group (**2b** vs **2a**).

Scheme 2. Substrate Scope[a]



1 **2**



[a]Reaction was conducted on **1** (0.2 mmol) in TFE (2.0 mL) under 50 bar of H_2 at rt for 24 h, in the presence of $[Ir(cod)Cl]_2$ (0.5 mol %), **L1** (2.2 mol %), and I_2 (10 mol %). Isolated yield. Ee was determined by chiral HPLC analysis.

Substrates with a phenyl R^1 group possessing electron-withdrawing or electron-donating substituents at the *para*- or *meta*-position could be reduced with 82−93% ee (**2c**−**2i**). A substrate bearing a Me group at the *ortho*-position of the phenyl ring was reduced to **2j** with a lower enantioselectivity of 76% ee. Substrates bearing a 2-naphthyl and 3,4-methylenedioxy group on the phenyl ring, and alkyl cyclohexyl groups, were reduced to their corresponding products **2k**, **2l**, and **2m** with 94%, 87%, and 70% ee, respectively. Additionally, we also applied our catalytic system to the asymmetric reduction of *γ*-

DOI: 10.1021/acs.orglett.7b00651
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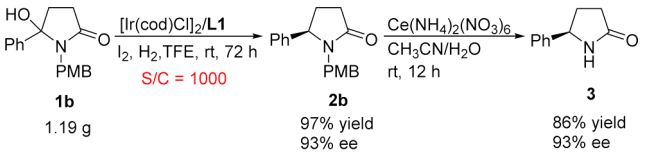
hydroxy γ-lactams bearing 3,3-dimethyl substituents because γ-lactams bearing 3,3-dimethyl substituents are useful building blocks for the synthesis of bioactive molecules and chiral auxiliaries (Scheme 2).[14] When the R^2 group on the nitrogen atom was Me, Et, Bn (benzyl), PMB, or DMPM (3,4-dimethoxybenzyl), the reduced products **2n**−**2r** were obtained with 90−94% ee. Substrates with a phenyl R^1 group bearing various substituents at different positions on the phenyl ring were reduced to the corresponding products **2s**−**2w** with 90−95% ee. A substrate possessing a 2-naphthyl group gave its reduced product **2x** with 96% ee. The absolute configuration of **2a** was determined as *R* by comparison with our previously published results.[10k]

The practicality of our developed catalytic system for the asymmetric reduction of γ-hydroxy γ-lactams was evaluated. The catalytic reaction was carried out at a low catalyst loading (S/C = 1000) on a gram scale, and the reduced product **2b** was obtained with 93% ee in 72 h, with no loss in enantioselectivity (Scheme 3). The product **2b** was transformed to compound **3**

Scheme 3. Gram-Scale Preparation of 2b and Its Transformation



via removal of the *N*-protecting group. According to literature reports, compound **3** can be transformed to various bioactive compounds, such as cannabinoid receptor 1 inhibitor **4**,[15] bioavailable tankyrase inhibitor **5**,[16] TNF activity modulator **6**,[17] and plant growth regulator **7**[18] (Figure 1).

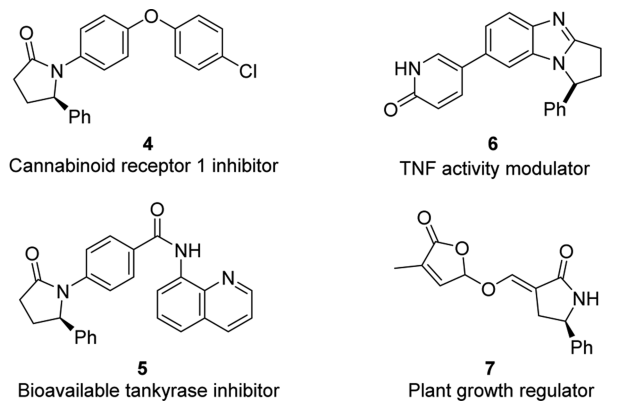
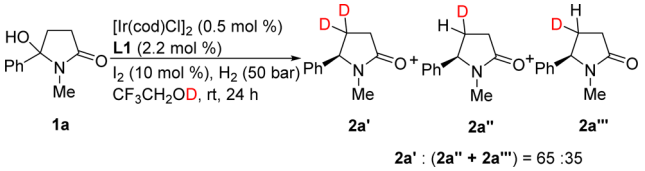


Figure 1. Potential bioactive compounds can be synthesized from **3**.

To gain deeper insight into the reaction pathway, a deuterium-labeling experiment was conducted (Scheme 4).

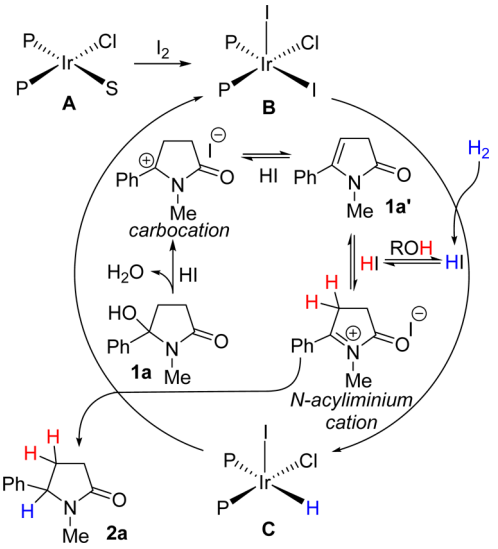
Scheme 4. Deuterium-Labeling Experiment



The use of CF_3CH_2OD as the reaction solvent afforded β-deuterated products **2a′**, **2a″**, and **2a‴**, with the ratio of **2a′** to **2a″** and **2a‴** being 65:35. This result differs slightly from our original mechanistic hypothesis (Scheme 1).

Based on the above experimental results and according to literature data,[10k,13a] a catalytic cycle for the iridium-catalyzed asymmetric reduction of γ-hydroxy γ-lactams has been proposed (Scheme 5). The oxidative addition of I_2 to Ir(I)

Scheme 5. Proposed Reaction Mechanism



precursor **A** generates the Ir(III) complex **B**, which could lead to heterolytic cleavage of H_2 and the generation of Ir(III)−H species **C** and HI. Compound **1a** then undergoes transformation to the carbocation in the presence of HI. According to the results of the deuterium-labeling experiments, it can be seen that almost all of the carbocation is transformed to β,γ-unsaturated γ-lactam **1a′**. In the presence of HI, the *N*-acyliminium cation is generated via protonation and isomerization of **1a′**. Hydride transfer from complex **C** to the *N*-acyliminium cation gives the reduced product **2a** and regenerates the Ir(III) complex **B**. A small amount of the carbocation may be reduced directly by Ir(III)−H species **C**, giving the reduced product with lower enantioselectivity. This is most likely responsible for the slight differences observed in the enantioselectivities of the iridium-catalyzed asymmetric reduction of β,γ-unsaturated γ-lactam and γ-hydroxy γ-lactam products.

In summary, an iridium-catalyzed asymmetric reduction of γ-hydroxy γ-lactams for the preparation of chiral γ-lactams was designed based on the reaction mechanism of our previous work. The chiral γ-lactams can be readily obtained in excellent yields and enantioselectivities. The reaction was also successful at a reduced catalyst loading of 0.1 mol % on a gram scale, and the resulting reduced product can be transformed to four bioactive compounds. Deuterium-labeling experiments confirmed that the reduced products were obtained via the hydrogenation of the *N*-acyliminium cationic intermediates which are generated via the elimination, protonation, and isomerization of γ-hydroxy γ-lactams. The reaction proceeds through a formal asymmetric hydrogenolysis of γ-hydroxy γ-lactams.

DOI: 10.1021/acs.orglett.7b00651
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00651.

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra, HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was partially supported by the National Natural Science Foundation of China (No. 21232004, 21372152, 21472123, and 21672142), Program of Shanghai Subject Chief Scientists (No.14XD1402300), the Basic Research Foundation of Shanghai Science and Technology Committee (15JC1402200), and the Instrumental Analysis Center of SJTU for characterization.

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DOI: 10.1021/acs.orglett.7b00651
Org. Lett. XXXX, XXX, XXX−XXX