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Rhodium-catalyzed intramolecular reductive aldol-type cyclization: Application for the synthesis of a chiral necic acid lactone.

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Abstract

Rhodium-catalyzed intramolecular reductive aldol-type cyclization was described to give β-hydroxylactones with high diastereoselectivities. This cyclization gave *syn*- or *anti*-form β-hydroxylactones selectively by changing the solvent. Furthermore, the synthesis of a chiral necic acid lactone was also described which is a part of structural

component of pyrrolizidine alkaloid monocrotaline that is used for the preparation of pulmonary hypertension pathological model in rats.

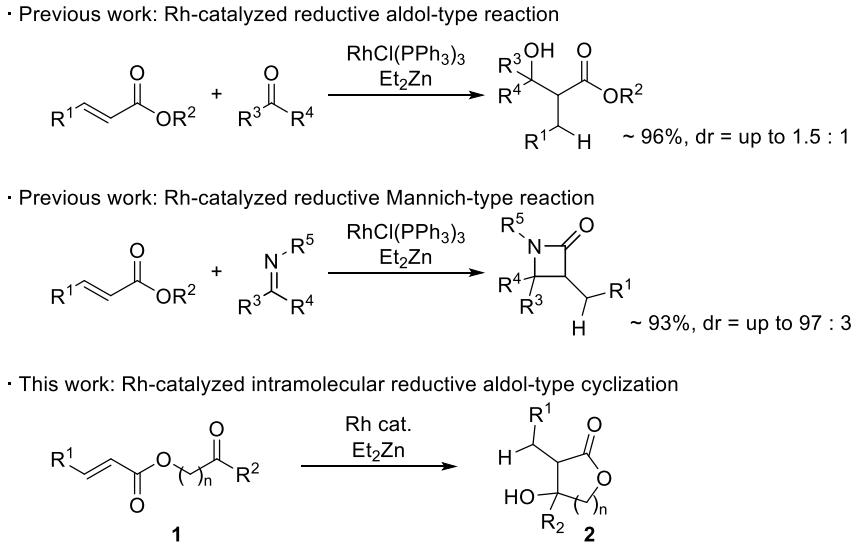
Keywords

intramolecular reductive aldol cyclization; β-hydroxylactone; rhodium catalyst; necic acid lactone

Introduction

During the past two decades, numerous numbers of the C–C bond formation reactions have been reported, and aldol reaction is one of the most powerful tools to achieve the reaction.[1] In particular, an intramolecular aldol condensation is an important approach to the formation of ring systems to give cyclic β-hydroxy carbonyl products or cyclic α,β-unsaturated carbonyl products. Therefore, various types of intramolecular aldol-type reaction have been developed and widely applied to the total synthesis of diverse natural products.[2] A reductive aldol-type reaction is also reported by using metal catalysts with hydrosilanes (R_3Si-H) or hydrogen as the reductant, and there are a lot of reports using rhodium catalyst.[3-10] However, there is still room for further investigation in this field, and we have reported reductive α-acylations, reductive aldol-type reactions, and reductive Mannich-type reactions using $RhCl(PPh_3)_3$ with Et_2Zn.[11] The rhodium-catalyzed reductive aldol reaction of α,β-unsaturated esters with aldehydes or ketones gave aldol-type products in good to excellent yields (Scheme 1).[11c,d] In addition, the reductive aldol-type reaction could also be applied to asymmetric system, although the diastereoselectivity was poor. On the other hand, the reductive Mannich-type reaction was achieved in good to excellent yields with high diastereoselectivity.[11e,f] As part of a wider program of C–C bond formation systems,

we report a rhodium-catalyzed intramolecular reductive aldol-type cyclization using a rhodium catalyst and its application for the synthesis of a chiral necic acid lactone.



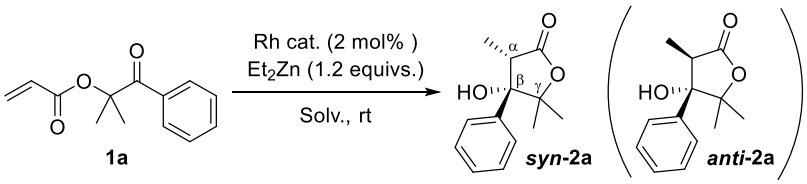
Scheme 1: Previous works and this work.

Results and Discussion

Rh catalyzed intramolecular cyclization

To improve the diastereoselectivity, at first, we optimized the conditions for the reductive aldol-type reaction by intramolecular cyclization of **1** (Table 1). According to the previous condition[11c], the intramolecular reductive aldol-type cyclization of **1a** proceeded smoothly and gave the desired product (**2a**) in a good yield but the diastereomeric ratio was not sufficient as shown in entry 1. After further examination of several rhodium catalysts, we found $[RhCl(cod)]_2$ was the best result with high diastereoselectivity (entries 1–4). A reduction by rhodium hydride complex was followed by transmetalation towards the corresponding Zn enolate to give the products with high diastereoselectivity in this cyclization. It is known that the formation of reductive enolate to α, β-unsaturated ester using metal hydride is influenced by steric factors around the reaction point. Therefore, it is considered that the use of

$[RhCl(cod)]_2$ having a soft ligand improved the diastereoselectivity as compared with the reaction using $RhCl(PPh_3)_3$. The stereochemistry in major product **2a** was *syn*-form between CH_3 (C^{α}) and OH (C^{β}) moieties and was established from the single-crystal X-ray structure analysis. When THF or DCM was used as the solvent, ***syn*-2a** was obtained in good yields with high diastereoselectivity as shown in entries 5–11. Interestingly, using higher coordination solvents, DMF or DMPU, preferentially gave the opposite diastereomer, and the major stereochemistry between CH_3 (C^{α}) and OH (C^{β}) moieties in **2a** was *anti*-form. A NOESY experiment on the ***syn*-2a** showed nOe between the methine proton on C^{α} and one of the protons of the benzene ring on C^{β}, but not ***anti*-2a**. The relative configurations of ***syn*-2a** and ***anti*-2a** were also confirmed by X-ray crystallography.



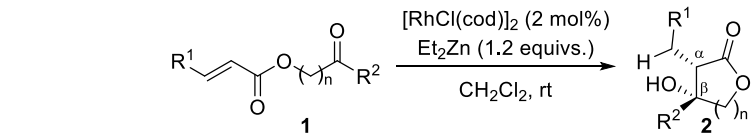
Entry	Rh cat.	Solv.	Time (h)	Yield (%)[a)]	Dr [*syn*:*anti*][b,c)]
1	$RhCl(PPh_3)_3$	THF	1	64	[3:1]
2	$[RhCl(cod)]_2$	THF	1.5	72	[30:1]
3	$RhClCO(PPh_3)_2$	THF	1	85	[9:1]
4	$Rh(acac)(CO)_2$	THF	1	trace	—
5	$[RhCl(cod)]_2$	Toluene	1	68	[14:1]
6	$[RhCl(cod)]_2$	AcOEt	1	79	[25:1]
7	$[RhCl(cod)]_2$	CH_2Cl_2	1	77	[31:1]
8	$[RhCl(cod)]_2$	DME	2	17[d)]	—
9	$[RhCl(cod)]_2$	CH_3CN	1	71	[2:1]
10	$[RhCl(cod)]_2$	DMF	3	42	[1:27]
11	$[RhCl(cod)]_2$	DMPU	1	52	[1:50]

a) Isolated yield.
b) The stereochemistry between CH_3 (C^{α}) and OH (C^{β}) moieties.
c) Diastereomeric ratio was determined after purification.
d) Diastereomeric mixture.

Table 1: Optimization of the reaction conditions.

Next, various substrates were investigated and the results were summarized in Table 2. The synthesis of **2a**-**c** proceeded smoothly to give the corresponding β-

hydroxylactones (**2**) in moderate to good yields with high diastereoselectivities, although **2d** were obtained in low yields. It may suggest that the existence of substituent(s) in γ-position and/or δ-position of **2** become easier to keep the intermediate structure which works in favor of the intramolecular cyclization. β-Substituted substrates on α,β-unsaturated ester moiety of **1** also gave the products (**2g** and **2h**) in low yields, but the formation of 7-membered ring (**2f**) was not achieved. On the other hand, when the previous condition using $RhCl(PPh_3)_3$ catalyst was applied to the aldol-type cyclization, 5- and 6-membered products were obtained in good yields (See the yields and dr in parentheses in Table 2). However, the yields were greatly affected by the substituents on β-position of α,β-unsaturated ester moiety, and all diastereomeric ratios were not sufficient results in the case of $RhCl(PPh_3)_3$ catalyst. The relative configurations of **2b** was confirmed by X-ray crystallography, and the relative configurations of **2c**, **2g** and **2h** were confirmed by NOESY experiments.



2a	**2b**	**2c**	**2d**
1h, 77%[a] [31:1][b] (64%[a] [3:1][b])[e]	2h, 80%[a] (79%[a,d])[e]	1h, 59%[a] (76%[a,d])[e]	2h, 27%[a,d] [18:1][c] (70%[a,d] [4:1][b])[e]

2e	**2f**	**2g**	**2h**	**2i**
1h, 15%[a,d] [2:3][c] (nd)[e]	13h, nd (trace[a])[e]	1.5h, 31%[a] (10%[a,d])[e]	3h, 20%[a] (trace[a])[e]	3h, nd (3h, nd)[e]

a) Isolated yield. b) Diastereomeric ratio was determined after purification.
c) Diastereomeric ratio was determined by ^1H NMR. d) Diastereomeric mixture.
e) The reaction was carried out using $RhCl(PPh_3)_3$ in THF at rt.

Table 2: Scope and limitation of the rhodium-catalyzed reductive aldol-type cyclization.

Synthesis for a chiral necic acid lactone of monocrotaline

There are a lot of reports for the bio-active natural products that have a 3-hydroxy-2-methyllactone scaffold in the molecular. For example, cytospolide K2 [12] containing a 10-membered lactone and feigrisolide [13] containing a 7-membered lactone are known to exhibit cytotoxicity and antimicrobial activity. Moreover, antiviral activity was also confirmed for aggregatin B [14] containing a 7-membered lactone ring, in which the β-position hydroxyl group was dehydrated (Fig. 1). Among them, monocrotaline that is a kind of pyrrolizidine alkaloid was isolated from seeds of *Crotalaria spectabilis* in 1935 and is used for the preparation of pulmonary hypertension pathological model rats.[15] To date, some groups have reported the synthetic method and its synthetic supply will be contributed to hypertension treatment.[16] Although there have been a lot of reports of pyrrolizidine scaffolds or necine base, the synthesis of necic acid lactones such as monocrotalic acid is rare (Fig. 2). Consequently, we attempted to apply the rhodium-catalyzed intramolecular reductive aldol-type reaction to the synthesis of a chiral necic acid lactone that is a part of structural component of monocrotaline.

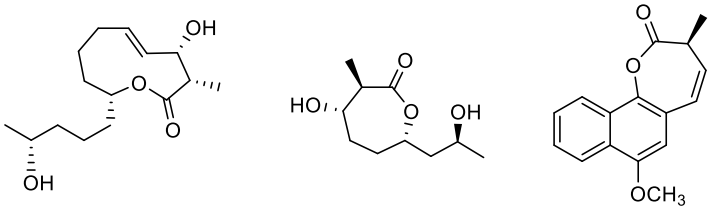


Fig. 1: Bio-active natural products bearing 3-hydroxy-2-methyllactone scaffold.

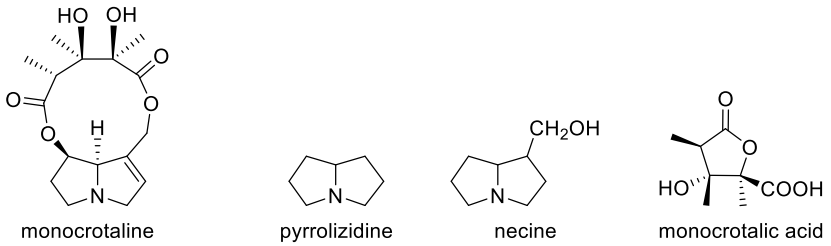
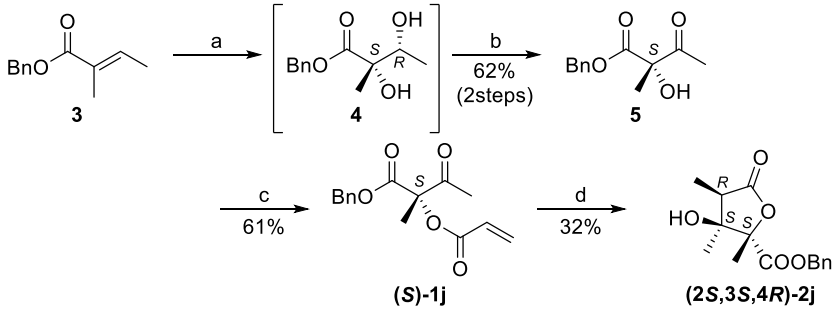


Fig. 2: Monocrotaline and its structural components.

According to the reference, Sharpless dihydroxylation of benzyl tiglate **3** to form a chiral diol **4** was followed by oxidation by Parikh-Doering oxidation to give the corresponding product **5** in 62% (Scheme 2).[17] Subsequent acryloylation in the presence of DMAP and hydroquinone gave the intramolecular cyclization starting material (*S*)-**1j** in 61% yield. The application of the compound (*R*)-**1j** to rhodium-catalyzed intramolecular reductive aldol-type cyclization was proceeded smoothly and gave a chiral necic acid lactone (2*S*,3*S*,4*R*)-**2j** in 32% yield (Fig. 3).



a) $CH_3SO_2NH_2$, AD-mix-β, *t*-BuOH, H_2O. b) SO_3•Py, Et_3N, DMSO, CH_2Cl_2.
c) DMAP, CH_2Cl_2, Et_3N, acryloyl chloride, hydroquinone. d) $[RhCl(cod)]_2$, THF, Et_2Zn.

Scheme 2: Synthetic route for a chiral necic acid lactone ((2*S*,3*S*,4*R*)-**2j**).

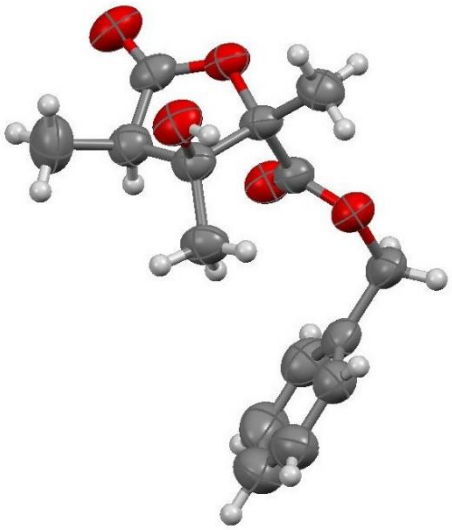


Fig. 3: Molecular structure of necic acid lactone ((2*S*,3*S*,4*R*)-**2j**) in the crystal.

Conclusion

In conclusion, we found that using $[RhCl(cod)]_2$ improved the diastereomeric ratios for the application to the intramolecular reductive aldol-type cyclization. It seems that using $[RhCl(cod)]_2$ becomes milder the reaction condition than using $RhCl(PPh_3)_3$, and therefore the diastereomeric ratios were greatly improved. In addition, we achieved a new approach to benzyl monocrotalate as the component of monocrotalin. We expect further progress for the study of intramolecular reductive aldol-type reaction.

Experimental

See Supporting Information File for full experimental data.

Supporting Information

General procedures and analytical data, including copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR spectra, and X-ray crystallography.

Supporting Information File 1:

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