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Diastereoselective radical addition to γ-alkyl-α-methylene-γ-butyrolactams and the synthesis of a chiral pyroglutamic acid derivative

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Full Research Paper

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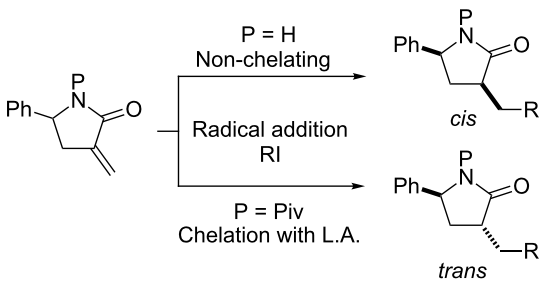
Abstract

The *cis*- and *trans*-stereoselective radical additions to α-methylene-γ-alkyl- γ-lactams were investigated and the scope and limitation of the reaction were also revealed. This stereoselective radical reaction was used for synthesis of chiral pyroglutamic acid derivatives starting from a commercially available chiral amino acid.

Introduction

γ-Lactams exist in many natural products and biologically active compounds and are one of the most important classes of compounds for drug discovery [1-3]. Substituted γ-lactams, in particular, have potential application in drug synthesis, but the development of stereoselective synthesis of chiral γ-lactams remains a challenge [4,5]. Developing effective and simple synthetic methods is important so that the drug candidates can be screened. A stereoselective addition to a γ-lactam skeleton provides a direct and efficient method for synthesizing various γ-lactam derivatives. However, the most commonly used methods for synthesizing chiral γ-lactams are based on the cyclization or cycloaddition of *N*-containing precursors, which are synthesized stereoselectively, and there are limited studies on the stereoselective additions to γ-lactam skeletons [6-8] and no reports on radical addition.

We have already investigated diastereoselective alkyl radical additions to α-methylene-γ-phenyl- γ-lactam and reported that the *N*-unsubstituted lactam yields *cis*-α,γ-disubstituted lactams using $(Me_3Si)_3SiH$ under UV irradiation, whereas the reactions of *N*-pivaloyllactams with Et_3B and Bu_3SnH in the presence of $Yb(OTf)_3$ yields *trans*-α,γ-disubstituted lactams, both reactions involving various alkyl radicals (Scheme 1) [9]. Although this method allows the stereoselective introduction of various substituents into γ-lactams, only γ-phenyl-γ-lactam was used as a substrate. Therefore, we were interested in whether our reac-



Scheme 1: Radical addition to α-methylene-γ-phenyl-γ-butyrolactams.

tion conditions would be suitable for γ-alkyl substrates and would allow the efficient synthesis of chiral *N*-containing compounds.

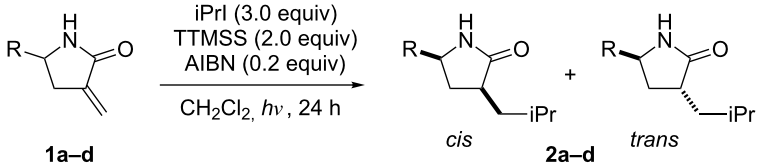
Here, we report *cis*- and *trans*-stereoselective radical additions to α-methylene-γ-alkyl- γ-lactams and the synthesis of chiral pyroglutamic acid derivatives using our reaction, starting from a commercially available chiral amino acid.

Results and Discussion

First, *cis*-selective isopropyl radical additions to α-methylene-γ-alkyl-γ-lactams were investigated (Table 1). The lactams **1a**–**1d** were synthesized following published procedures [10]. The conditions used in our previous study [9] were used as the starting point, and the reactions of **1a**–**1d** (1 equiv) with isopropyl iodide (3 equiv) in CH_2Cl_2 by using AIBN (0.2 equiv) as a radical initiator and $(Me_3Si)_3SiH$ (TTMSS) (2 equiv) as a H-donor were performed at room temperature under UV irradiation. The reactions of **1a** and **1b** yielded strong *cis*-diastereoselectivities, but the reactions of **1c** and **1d** were less diastereoselective.

Next, isopropyl radical additions to *N*-pivaloyl substrates **3a**–**3d** in the presence of a Lewis acid were investigated (Table 2). The

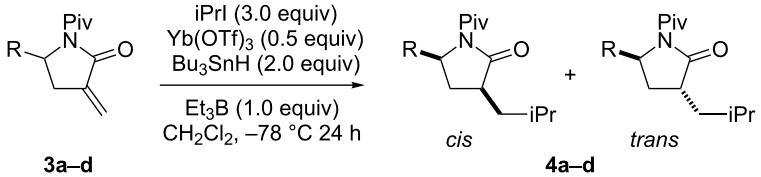
Table 1: Radical addition to **1** under non-chelating conditions.



1a–d **2a–d**

entry	**1**	R	**2**	yield (%)	*cis*/*trans*
1	**1a**	iPr	**2a**	82	91:9
2	**1b**	*c*-Hex	**2b**	55	92:8
3	**1c**	iBu	**2c**	52	80:20
4	**1d**	$PhCH_2CH_2$	**2d**	49	84:16

Table 2: Radical addition to **3** under chelating conditions.



3a–d **4a–d**

entry	**3**	R	**4**	yield (%)	*cis*/*trans*
1	**3a**	iPr	**4a**	90	45:55
2	**3b**	*c*-Hex	**4b**	42	75:25
3[a]	**3b**	*c*-Hex	**4b**	62	88:12
4[b]	**3b**	*c*-Hex	**4b**	46	80:20
5	**3c**	iBu	**4c**	85	36:64
6	**3d**	$PhCH_2CH_2$	**4d**	71	50:50

[a]Without $Yb(OTf)_3$. [b]1.0 equiv of $Yb(OTf)_3$ was used.

reactions of **3a**–**3d** (1 equiv) with isopropyl iodide (3 equiv) in CH_2Cl_2 in the presence of Et_3B (1 equiv), Bu_3SnH (2 equiv), and $Yb(OTf)_3$ (0.5 equiv) were performed at −78 °C. The reactions of **3a**, **3c,** and **3d** were almost nondiastereoselective, while that of **3b** was *cis*-selective. The selectivity was almost the same as when the reaction was performed without a Lewis acid (Table 2, entry 3). Using an excess of $Yb(OTf)_3$ did not affect the diastereoselectivity (Table 2, entry 2).

We then changed the protecting group of the lactam nitrogen from the pivaloyl to the acetyl group and investigated the reaction in the presence of a Lewis acid (Table 3). The reactions of **5c** and **5d** yielded strong *trans*-selectivities, but *cis*-selectivities were observed in the reactions of **5a** and **5b**. The use of $MgBr_2$–OEt_2 instead of $Yb(OTf)_3$ enhanced the yield but did not affect the diastereoselectivity (Table 3, entry 2).

The direction of hydrogen transfer from the H-donor (*n*-Bu_3SnH or TTMSS) to the intermediate radical determined the stereochemistry of the product. In the case of the reaction of unprotected lactam by using a bulky H-donor (Table 1), hydrogen transferred from the opposite side of the γ-alkyl group and the *cis*-product was obtained. The less hindered primary isobutyl or phenethyl substrates (**1c** or **1d**) yielded poorer stereoselectivities than did **1a** or **1b**. *Trans*-selectivity was expected for the amide type *N*-protecting group reaction because of the coordinating carbonyl oxygens. The carbonyl oxygen of lactam and that of the *N*-protecting group (pivaloyl or acetyl) bidentately coordinate to the Lewis acid to form a six-membered chelate. The Lewis acid coordinates from the opposite side of the γ-alkyl group, and hydrogen transfer occurred from the same face as the γ-alkyl substituent to give *trans*-selectivity. However, strong *trans*-selectivities were not observed for substrates with pivaloyl groups, and it appears that steric hindrance between the pivaloyl group and the lactam γ-alkyl disturbs chelation. Using the acetyl group, which is less sterically hindered than the pivaloyl group, improved the chelate formation of γ-isobutyl or γ-phenethyl substrates and the reactions of **5c** and **5d** were *trans*-selective. In contrast, relatively bulky isopropyl or cyclohexyl groups could not form the six-membered chelate because of the steric repulsion between the acetyl and tertiary alkyl group (Figure 1).

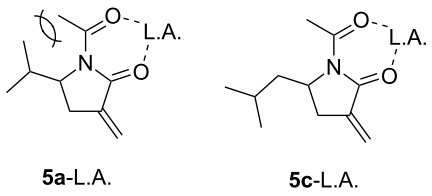
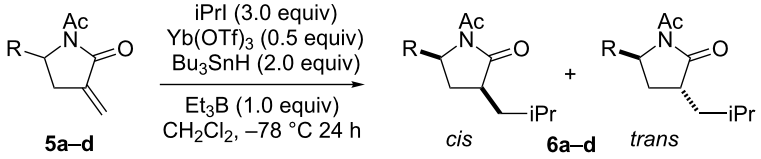


Figure 1: Chelation of **5a** and **5d**.

Finally, we attempted to synthesize the chiral pyroglutamic acid derivatives starting from a commercially available chiral amino acid. The reaction of benzaldehyde and (*S*)-phenylglycinol in the presence of $MgSO_4$ (used as a dehydrating reagent) gave a chiral imine, and the subsequent Reformatsky reaction with bromide **7** afforded butyl acrylate **8** as a single diastereomer [11,12] (Scheme 2). Hydrolysis with CF_3CO_2H and converting the hydroxy group to the chloride yielded the corresponding lactam **9** [13]. The chiral auxiliary was removed by DBU-assisted elimination to the enamine and subsequent hydrolysis [14]. Introducing the pivaloyl group, because *N*-pivaloyl gave high trans-selectivity of γ-phenyl substrate, yielded the chiral radical substrate **10**.

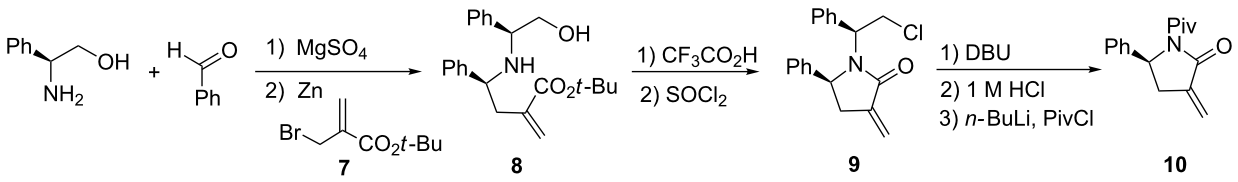
The *trans*-selective ethyl radical addition proceeded, yielding **11** with high diastereoselectivity, as we previously reported [9]. The *trans*-isomer was isolated by silica-gel column chromatography. The *N*-pivaloyl group on **11** was converted to the Boc

Table 3: Radical addition to **5** under chelating conditions.

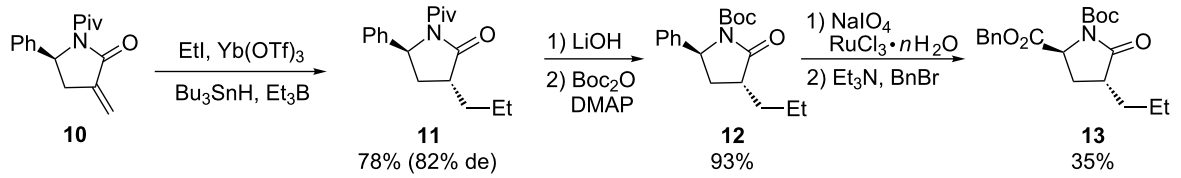


entry	5	R	6	yield (%)	*cis*/*trans*
1	**5a**	iPr	**6a**	37	78:22
2[a]	**5a**	iPr	**6a**	84	66:39
3	**5b**	*c*-Hex	**6b**	51	62:38
4	**5c**	iBu	**6c**	97	20:80
5	**5d**	$PhCH_2CH_2$	**6d**	92	25:75

[a]3.0 equiv of $MgBr_2$–OEt_2 was used instead of $Yb(OTf)_3$.



Scheme 2: Synthesis of chiral substrate **10**.



Scheme 3: Synthesis of chiral 4-butyl-L-pyroglutamic acid **13**.

group, because ruthenium oxidation did not proceed on using the pivaloyl-protected substrate **11**. The phenyl group was oxidized to the carboxylic acid by using ruthenium trichloride [15,16], and the benzylation of the carboxyl group yielded the pyroglutamic acid derivative **13** as a single stereoisomer (Scheme 3).

Conclusion

In this study, we investigated the *cis*- and *trans*-stereoselective radical additions to α-methylene-γ-alkyl- γ-lactams. Strong *cis*-selectivities were observed using various γ-substituents under non-chelating conditions. The reactions of pivaloyl protected substrates in the presence of a Lewis acid were not *trans*-selective, although pivaloyl protected γ-phenyl substrates gave high *trans*-selectivity in our previous report. The poor selectivities were attributed to the steric repulsion between the pivaloyl group and the γ-substituent on the substrate. The reactions using *N*-acetyl substrates instead of pivaloyl substrates yielded better *trans*-selectivities with γ-isobutyl and γ-phenethyl substrates, because acetyl is sufficiently small to allow chelation with the Lewis acid and lactam carbonyl. We used the reaction to synthesize chiral pyroglutamic acid derivatives starting from (*S*)-phenylglycinol.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data for compounds **2a**–**d**, **6a**–**d** and **9**–**13**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-9-161-S1.pdf]

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