Asymmetric synthesis of β-lactams using chiral-memory effect on photochemical γ-hydrogen abstraction by thiocarbonyl group†

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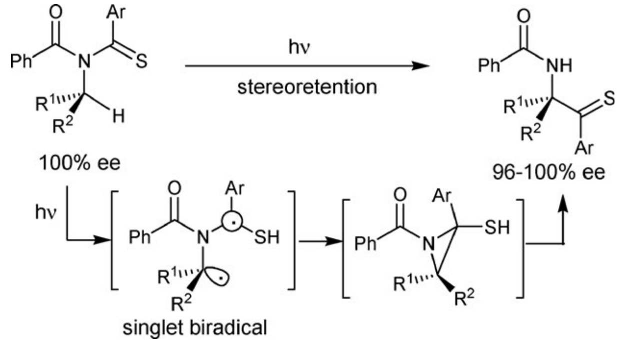
Optically active β-lactams were synthesized *via* photochemical intramolecular γ-hydrogen abstraction reaction of thioimides involving a highly-controlled chiral-memory effect.

Recently, we reported the enantioselective synthesis of chiral quaternary carbons from commercially available chiral amines and amino acids using the chiral-memory effect *via* the photochemical β-hydrogen abstraction reaction by a thiocarbonyl group (Scheme 1).[1] In the reaction, in spite of the radical center being generated at the original chiral center, the chirality was retained because the reaction proceeded from the singlet excited state of the thiocarbonyl group. It is well known that molecules in the singlet state mostly react more stereoselectively than the corresponding triplet state molecules because the singlet state molecules react faster than molecular motions such as bond rotation.[2] Giese *et al.* reported a stereospecific photochemical route to proline derivatives by a singlet Norrish–Yang photocyclization reaction *via* a 1,5-biradical intermediate generated by δ-hydrogen abstraction of glyoxalate derivatives.[3] The reaction is one of the few remarkable examples of the photochemical "chiral-memory effect."[4,5] Griesbeck *et al.* reported that the photocyclization involving γ-hydrogen abstraction of phenylglyoxalylamide derivatives lost the chirality of the starting materials and gave racemic β-lactams.[6] Now we have studied the synthesis of optically active β-lactams using the chiral memory effect on γ-hydrogen abstraction of thiocarbonyl groups of thioimides.

Thioimides show considerably high photochemical reactivity toward hydrogen abstraction by the thiocarbonyl sulfur from the β-, γ- and δ-positions, and the reaction provides a useful synthesis of several types of heterocyclic compounds.[7] In photochemical γ-hydrogen abstraction of acyclic monothioimides, β-lactams were obtained *via* a 1,4-diradical intermediate.[8] Then, the asymmetric photochemical reaction of monothioimides derived from optically active 2-phenylpropanoic acid was studied (Scheme 2). If the lifetime and the flexibility of the diradical intermediate are low, the chiral-memory effect will be observed, and an enantioselective photochemical reaction should occur.

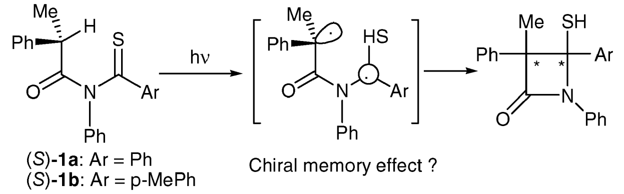


Scheme 1 Asymmetric synthesis of quaternary carbons *via* chiral memory effect on β-hydrogen abstraction by the thiocarbonyl group.

Optically active monothioimides ((S)-**1a,b**) were prepared by acylation of the corresponding thioaroylanilides. The optical activity of (*S*)-2-phenylpropanoic acid was not lost through chlorination by $SOCl_2$ followed by the reaction with thioaroylanilides in the presence of triethylamine. The 96% ee of **1a,b** was used for the asymmetric photoreaction.

Both monothioimides have absorptions derived from ππ* excitation in the UV region and from nπ* excitation of the thiocarbonyl group in the visible region (430–570 nm).

When a 20 mM toluene solution of (*S*)-**1a** was irradiated with Pyrex-filtered light from a 500-W high-pressure mercury lamp under argon atmosphere, the product analysis indicated the formation of two stereoisomeric 4-mercapto-β-lactams **2a** accompanied by a small amount of benzthioanilide **3a**. The enantiomeric excesses of two stereoisomeric isomers of **2a** were analyzed by HPLC using a CHIRALCEL AD-H column (Daicel Industry), which showed that the ee values were 96 and 95%, for (3*R*,4*S*)-**2a** and (3*R*,4*R*)-**2a**, respectively (Table 1, entry 1). The absolute configuration of (3*R*,4*S*)-**2a** was determined as the *S*-acetyl derivative (3*R*,4*S*)-4-acetylthio-3-methyl-1,3,4-triphenylazetidin-2-one **4a** by the X-ray anomalous dispersion method.[9] The structures of other β-lactams were determined on the basis of spectral data, and the



Scheme 2 Photochemical β-lactam synthesis by γ-hydrogen abstraction by a thiocarbonyl group.

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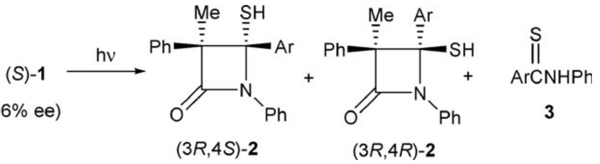
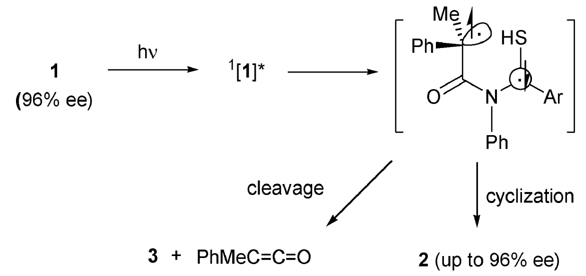
Table 1 Photochemical reaction of **1a,b** under various conditions



Entry	Imide **1**	Yield[c] (%) of (3*R*,4*S*) **2**	Ee (%) of (3*R*,4*S*)-**2**	Yield[c] (%) of (3*R*,4*R*)-**2**	Ee (%) of (3*R*,4*R*)-**2**	Yield[d] (%) of **3**
1[a]	(*S*)-**1a**	50	96	11	95	21
2[a]	(*S*)-**1b**	59	93	10	85	23
3[b]	(*S*)-**1b**	56	96	13	94	15

[a] A 20 mM toluene solution was irradiated with a 500-W high-pressure mercury lamp through a Pyrex filter. [b] A 50 : 50 mixed solvent of *t*-BuOH and toluene was used for irradiation. [c] Chemical yields were determined by ^{1}H NMR. [d] Isolated yields.



Scheme 3 Photochemical γ-hydrogen abstraction of monothioimides **1**.

stereochemistry was analysed by the comparison of their spectral data with (3*R*,4*S*)-**2a** and (3*R*,4*R*)-**2a**.

Irradiation of other monothioimides (*S*)-**1b** in toluene solution also gave the corresponding mercapto-β-lactams **2b** in 59 and 10% chemical yields; furthermore, the optical activity was also retained as shown by the ee values of 93% for (3*R*,4*S*)-**2b** and 85% for (3*R*,4*R*)-**2b**, respectively (entry 2) although decreased a little relative to entry 1. The reaction using *t*-BuOH as a solvent gave the corresponding **2b** in higher ees (96 and 94%), respectively (entry 3). The back hydrogen transfer from the biradical intermediate gave rise to lowering the ee value by reversal reaction in a Type II process. In this case, it seems that the use of *t*-BuOH slowed down the back hydrogen transfer process from the biradical intermediate by forming a hydrogen bond with the mercapto group.[10]

The mechanism for the formation of β-lactams **2** and benzthioanilide **3** involves a 1,4-diradical intermediate generated by γ-hydrogen abstraction by the thiocarbonyl sulfur atom (Scheme 3). Sensitization of the reaction by a triplet sensitizer such as Michler's ketone or thioxanthone was quite inefficient. These results clearly indicate that the hydrogen abstraction reaction proceeds from the singlet excited state of thioimides. Short-lived diradical cyclizes rather faster than the racemization process owing to the bond rotation around the radical site.

In conclusion, optically active β-lactams were effectively synthesized *via* photochemical intramolecular γ-hydrogen abstraction of thioimides, where the highly-controlled chiral-memory effect was observed. This reaction provides not only the first example of a chiral-memory effect for the photochemical γ-hydrogen abstraction reaction of thiocarbonyl or carbonyl compounds, but also a useful synthetic methodology of optically active β-lactams.

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