

# Photochemical asymmetric synthesis of phenyl-bearing quaternary chiral carbons using chiral-memory effect on $\beta$ -hydrogen abstraction by thiocarbonyl group†

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Received (in Cambridge, UK) 16th June 2006, Accepted 30th August 2006

First published as an Advance Article on the web 25th September 2006

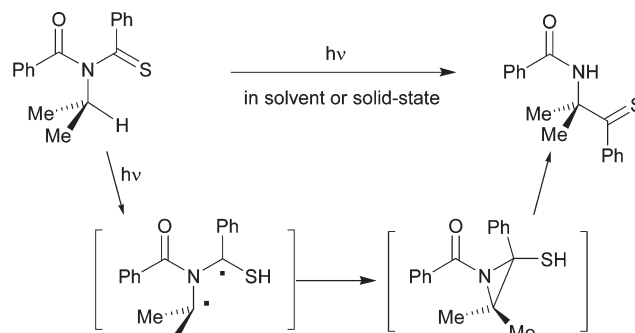
DOI: 10.1039/b608513j

Quaternary chiral carbons were effectively generated from tertiary chiral carbons *via* photochemical intramolecular  $\beta$ -hydrogen abstraction reaction of thioimides involving the highly-controlled chiral-memory effect.

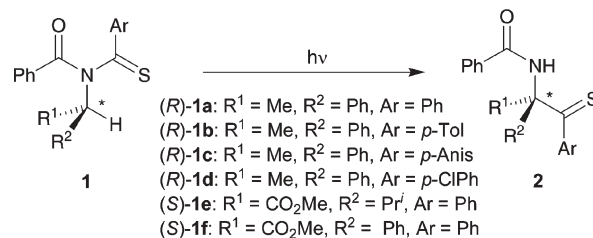
Reactions of spin-isomers, singlet or triplet, often lead to different products; molecules in the singlet state react mostly more stereoselectively than the corresponding triplet state molecules; the singlet state molecules react faster than molecular motion such as bond rotation.<sup>1</sup> Recently, Giese *et al.* reported a stereospecific photochemical route to proline derivatives by a singlet Norrish–Yang photocyclization reaction of glyoxalate derivatives.<sup>2</sup> The reaction is one of the few remarkable examples of the photochemical “chiral-memory effect”.<sup>3</sup> Now, we have tried to synthesize chiral quaternary carbons enantioselectively from commercially available chiral amines and amino acids using the chiral-memory effect *via* the photochemical hydrogen abstraction reaction by a thiocarbonyl group.

Photochemical hydrogen abstraction of thioketones has been extensively studied by de Mayo *et al.*,<sup>4</sup> and it was mentioned that the excited state of the reaction proceeded from both the  $S_2$  ( $\pi\pi^*$ ) state and the  $T_1$  ( $n\pi^*$ ) state. Like thioketones, thioimides show considerably high photochemical reactivity toward hydrogen abstraction by the thiocarbonyl sulfur, and the reaction provides a useful synthesis of several types of heterocyclic compounds.<sup>5</sup> In photochemical  $\beta$ -hydrogen abstraction of acyclic monothioimides, the isopropyl group was transformed to quaternary carbons *via* a 1,3-diradical intermediate and mercaptoaziridine as shown in Scheme 1.<sup>6</sup> In the reaction, the  $sp^3$  carbon centre is converted to a radical site, and then the  $sp^3$  carbon centre is regenerated. Now, we have studied the enantioselective photochemical reaction of monothioimides derived from optically active 1-phenethylamine and amino acid derivatives (Scheme 2). If the lifetime and the flexibility of the diradical intermediate are low, a chiral-memory effect will be observed and an enantioselective change will occur.

Enantiomerically pure monothioimides (*R*)-**1a–d** were easily prepared by benzylation of the corresponding (*R*)-*N*-(1-phenethyl)thioaroylamides. The derivatives (*S*)-**1e** and (*S*)-**1f**, possessing amino acid ester groups, were prepared from the methyl esters of L-valine and L-phenylglycine by benzylation, followed by



Scheme 1



Scheme 2

thionation and benzylation again. All monothioimides have absorptions arising from  $\pi\pi^*$  excitation in the UV region and from  $n\pi^*$  excitation of the thiocarbonyl group in the visible region (400–540 nm). Fig. 1 exemplifies the absorption spectrum of **1a** in cyclohexane ( $1.0 \times 10^{-4}$  M).

When a 20 mM toluene solution of (*R*)-**1a** was irradiated with Pyrex-filtered light from a 500 W high-pressure mercury lamp

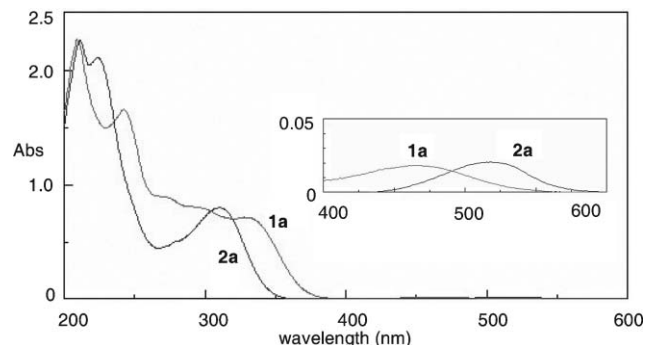


Fig. 1 Absorption spectra of (*R*)-**1a** and (*R*)-**2a**

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† Electronic supplementary information (ESI) available: Crystal data for **1a**, **1e**, **2a**, **2b**, **2d** and structure diagrams. See DOI: 10.1039/b608513j

**Table 1** Photochemical reaction of **1a–f** under various conditions

Entry	Thioimide <b>1</b>	Conditions	Conv. (%)	Yield (%)	Config. of <b>2</b>	Ee (%) of <b>2</b>
1	( <i>R</i> )- <b>1a</b>	Toluene <sup>a</sup>	100	97	<i>R</i> <sup>b</sup>	100
2	( <i>R</i> )- <b>1a</b>	solid-state	100	99	<i>R</i> <sup>b</sup>	100
3	( <i>R</i> )- <b>1b</b>	Toluene <sup>a</sup>	100	94	<i>R</i> <sup>b</sup>	97
4	( <i>R</i> )- <b>1b</b>	solid-state	100	96	<i>R</i> <sup>b</sup>	100
5	( <i>R</i> )- <b>1c</b>	Toluene <sup>a</sup>	100	97	<i>R</i> <sup>c</sup>	96
6	( <i>R</i> )- <b>1d</b>	Toluene <sup>a</sup>	100	96	<i>R</i> <sup>b</sup>	100
7	( <i>R</i> )- <b>1d</b>	Solid-state	100	95	<i>R</i> <sup>b</sup>	100
8	( <i>S</i> )- <b>1e</b>	Toluene <sup>a</sup>	0	0	—	—
9	( <i>S</i> )- <b>1e</b>	Solid-state	0	0	—	—
10	( <i>S</i> )- <b>1f</b>	Toluene <sup>a</sup>	45	91	<i>S</i> <sup>c</sup>	100

<sup>a</sup> A 0.02 M toluene solution was irradiated with a 500 W high-pressure mercury lamp through a Pyrex filter. <sup>b</sup> The absolute configuration was determined by X-ray structural analysis. <sup>c</sup> The absolute configuration was speculated on the basis of the configuration of starting materials and the reaction mechanism.

under an argon atmosphere, the orange solution turned reddish-purple with an absorption in the 450–580 nm region as shown in Fig. 1. The product analysis indicated the formation of thioketone **2a**. The enantiomeric excess of **2a** was analyzed by HPLC using CHIRALCEL AD-H column (Daicel industry), which showed that the ee value was 100% (Table 1, entry 1). The absolute configurations of both **1a** and **2a** were determined as (*R*)-isomers by the X-ray anomalous dispersion method.† Irradiation of other monothioimides (*R*)-**1b–d** in solution also effectively gave the corresponding thioketones (*R*)-**2b–d** in almost quantitative yields, and with 97–100% optical purity (entries 3, 5, and 6). However the thioimide (*S*)-**1e** derived from the L-valine ester was inert toward photolysis (entry 8), and irradiation of phenylglycine derivative (*S*)-**1f** gave the corresponding thioketone (*S*)-**2f** (entry 10). When the conversion was suppressed to 45%, the stereochemistry of the chiral carbon incorporated in the amino acid chromophore was controlled perfectly to form 100% ee of (*S*)-**2f**. The absolute configurations of (*R*)-**2b** and (*R*)-**2d** were also determined by the X-ray anomalous dispersion method. The configurations of other thioketones, (*R*)-**2c** and (*S*)-**2f**, were predicted on the basis of the configuration of the starting materials and the reaction mechanism.

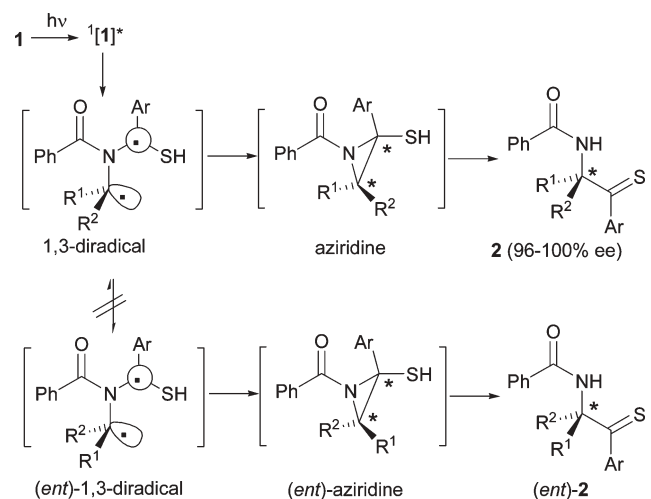
Solid monothioimides, **1a–b** and **1d–e**, were also irradiated in the solid-state. From the X-ray analysis, the imide (*R*)-**1a** has an *E,E* conformation, where the β-hydrogen atom inclines to the thiocarbonyl sulfur atom. The two atoms are closely placed at 2.52 Å, which is much shorter than the sum of the van der Waals radii (H, 1.20 Å; S, 1.80 Å). When powdered (*R*)-**1a**, well ground and sandwiched by Pyrex glass plates, was irradiated at room temperature, crystals gradually changed to amorphous according to the progress of the reaction; however, the reaction proceeded effectively and gave thioketone (*R*)-**2a** with 100% retained chirality. In the case of (*R*)-**1b**, the enantiomeric excess was 100%, which is higher than that of the solution photochemistry. Irradiation of (*R*)-**1d** also gave 100% ee of (*R*)-**2d** with perfect retention of stereochemistry by the chiral-memory effect.

The photoreaction of the monothioimide (*S*)-**1e** did not proceed even in the solid-state. X-Ray analysis of the monothioimide (*S*)-**1e** shows almost the same conformation as the photoreactive monothioimide **1a**. The *E,E* conformation is the favourable conformation for the hydrogen abstraction of the thiocarbonyl carbon from the β-position. The two atoms are closely placed at 2.59 Å, which is short enough for the hydrogen transfer. These facts indicate that the monothioimide (*S*)-**1e** has no ability of

hydrogen abstraction because of the absence of a strongly stabilizing substituent such as a phenyl group and the deleterious effect of the ester group. On the other hand, (*S*)-**1f**, possessing a phenyl group at the radical centre, showed high photochemical reactivity.

The mechanism for the formation of thioketones **2** involves a 1,3-diradical intermediate generated by β-hydrogen abstraction by the thiocarbonyl sulfur atom (Scheme 3). The short-lived diradical cyclizes faster than the racemization process as a result of the bond rotation around the radical site. The sensitization reaction with thioxanthone or Michler's ketone as the triplet sensitizer was quite inefficient. This fact indicates that the direct irradiation involves a singlet biradical and it cyclizes so fast that there is not enough time for the inversion of the biradical by the C–N bond rotation before the new C–C bond is formed. In the monothioimides, a benzoyl group attached to the nitrogen atom and the group on the pendant carbon are large, and the steric factor may also influence the rotation.

In conclusion, chiral quaternary carbons were effectively generated from tertiary chiral carbons *via* photochemical intramolecular β-hydrogen abstraction from the singlet excited state of thioimides where the highly-controlled chiral-memory effect was observed. This reaction provides not only the first example of chiral-memory effect for the photochemical reaction of



**Scheme 3** Plausible reaction mechanism with chiral memory effect *via* β-hydrogen transfer reaction of thioimides **1**.

thiocarbonyl compounds but also a useful synthetic methodology of optically active materials from easily available amines or amino acids.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Area (417) and a Grant-in-Aid for Scientific Research (No 1720511) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of the Japanese Government.

## Notes and references

‡ *Crystal data*: for (*R*)-**1a** (recrystallized from a mixture of CHCl<sub>3</sub> and hexane); C<sub>22</sub>H<sub>19</sub>NOS, *M<sub>r</sub>* = 345.44, orthorhombic, space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *a* = 6.126(3) Å, *b* = 9.050(4) Å, *c* = 32.991(11) Å, *V* = 1829.0(13) Å<sup>3</sup>, *Z* = 4, ρ = 1.255 Mgm<sup>-3</sup>; in the final least-square refinement cycles on *F*<sup>2</sup>, the model converged on *R*1 = 0.0440, *wR*2 = 0.1187 for 2052 reflections. Absolute structure parameter -0.02(4). CCDC 611153

*Crystal data*: for (*S*)-**1e** (recrystallized from a mixture of CHCl<sub>3</sub> and hexane); C<sub>20</sub>H<sub>21</sub>NO<sub>3</sub>S, *M<sub>r</sub>* = 355.44, monoclinic, space group *P*2<sub>1</sub>, *a* = 7.7515(8) Å, *b* = 12.0713(13) Å, *c* = 9.9335(10) Å, β = 97.9140(10)°, *V* = 920.70(17) Å<sup>3</sup>, *Z* = 2, ρ = 1.289 Mgm<sup>-3</sup>; in the final least-square refinement cycles on *F*<sup>2</sup>, the model converged on *R*1 = 0.0286, *wR*2 = 0.0759 for 3462 reflections. Absolute structure parameter 0.03(6). CCDC 611154

*Crystal data*: for (*R*)-**2a** (recrystallized from a mixture of CHCl<sub>3</sub> and hexane); C<sub>22</sub>H<sub>19</sub>NOS, *M<sub>r</sub>* = 345.44, orthorhombic, space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *a* = 9.857(3) Å, *b* = 11.082(3) Å, *c* = 17.126(5) Å, *V* = 1870.8(9) Å<sup>3</sup>, *Z* = 4, ρ = 1.266 Mgm<sup>-3</sup>; in the final least-square refinement cycles on *F*<sup>2</sup>, the model converged on *R*1 = 0.0612, *wR*2 = 0.1447 for 3956 reflections. Absolute structure parameter 0.08(3). CCDC 611155

*Crystal data*: for (*R*)-**2b** (recrystallized from a mixture of CHCl<sub>3</sub> and hexane), C<sub>23</sub>H<sub>21</sub>NOS, *M<sub>r</sub>* = 359.47, orthorhombic, space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *a* = 9.7025(7) Å, *b* = 9.9727(7) Å, *c* = 20.1303(15) Å, *V* = 1947.8(2) Å<sup>3</sup>, *Z* = 4, ρ = 1.229 Mgm<sup>-3</sup>; in the final least-square refinement cycles on *F*<sup>2</sup>, the model converged on *R*1 = 0.0372, *wR*2 = 0.0534 for 4445 reflections. Absolute structure parameter 0.03(5). CCDC 611156.

*Crystal data*: for (*R*)-**2d** (recrystallized from a mixture of CHCl<sub>3</sub> and hexane) C<sub>22</sub>H<sub>18</sub>CINOS, *M<sub>r</sub>* = 379.88, orthorhombic, space group *P*2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>, *a* = 9.6375(5) Å, *b* = 10.0167(5) Å, *c* = 20.0523(10) Å, *V* = 1935.77(17) Å<sup>3</sup>, *Z* = 4, ρ = 1.314 Mgm<sup>-3</sup>; in the final least-square refinement cycles on *F*<sup>2</sup>, the model converged on *R*1 = 0.0346, *wR*2 = 0.0746 for 4458 reflections. Absolute structure parameter -0.05(5). CCDC 611157

For crystallographic data in CIF or other electronic format see DOI: 10.1039/b608513j

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