

Chirality Transfer in Gold-Catalyzed Carbothiolation of *o*-Alkynylphenyl 1-Arylethyl Sulfides

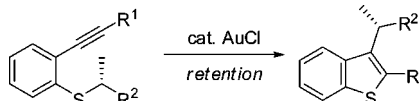
Itaru Nakamura,* Takuma Sato, Masahiro Terada, and Yoshinori Yamamoto

Department of Chemistry, Graduate School of Science, Tohoku University,
Sendai 980-8578 Japan

itaru-n@mail.tains.tohoku.ac.jp

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ABSTRACT



Chirality transfer in gold-catalyzed carbothiolation of *o*-alkynylphenyl 1-arylethyl sulfides **1** proceeded with retention of the configuration at the 1-arylethyl group. This result suggests that the [1,3] migration of 1-arylethyl group proceeds through formation of the contact ion pair **B** followed by C–C bond formation.

Catalytic cyclization is one of the most efficient methods to synthesize 2-monosubstituted indoles and benzofurans from *o*-alkynylanilines and -phenols (eq 1).¹ Recently, transition-metal-catalyzed cyclization of *o*-alkynylanilines, -phenyl ethers, and -phenyl sulfides bearing a migration group (E) on the heteroatom (Y) has attracted much attention as a direct method to synthesize the 2,3-disubstituted indoles,² benzofurans,^{2a,b,3} and benzo[*b*]thiophenes,⁴ which have been widely utilized

as medicines and organic materials (eq 2). It has been proposed that this reaction proceeds through a [1,3] shift of the migrating group on the heteroatom of the zwitterionic intermediate **A**. However, the nature of this [1,3] migration has rarely been elucidated to date. In this communication, we report that chirality transfer in the gold-catalyzed carbothiolation of *o*-alkynylphenyl 1-arylethyl sulfides **1** proceeds with retention of stereocenter at the 1-arylethyl group (eq 3).⁵

(*R*)-2-[[*p*-(*tert*-Butyldimethylsiloxy)phenyl]ethynyl]-phenyl 1-phenylethyl sulfide **1a**, which was prepared from Mitsunobu reaction of commercially available (*S*)-1-phenylethanol with 2-bromobenzenethiol followed by Sonogashira coupling, was reacted in the presence of 2 mol % of AuCl in toluene at 25 °C to afford **2a** in 94% yield with 79% chirality transfer (Scheme 1). The product **2a** was converted to the brosylate **3**, of which the absolute stereo configuration was unambiguously determined to be *R* by

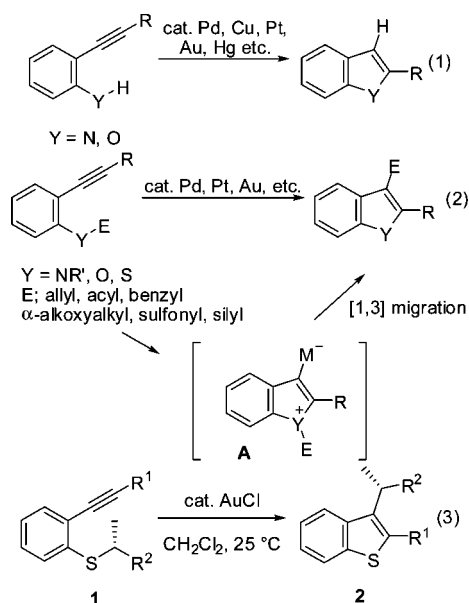
(1) For a review, see: (a) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198.

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X-ray crystallographic analysis (Figure 1).⁶ The present reaction is concluded to proceed with retention of the configuration at the α -phenethyl group.

Next, we explored the substrate scope of the gold-catalyzed chirality transfer reaction of **1** as summarized in Table 1. The reaction of **1b** having a *p*-anisyl group at the alkynyl moiety at 25 °C proceeded with a high level of chirality transfer (entry 1). Among the solvents we examined, we found that the use of CH₂Cl₂ gave the best result (see Supporting Information). Decrease of the ee of **2b** was observed in the reaction at 50 °C (entry 2). The reaction at 0 °C proceeded slowly, giving **2b** with 71% of chirality transfer (entry 3). The chirality of 1-(*p*-chlorophenyl)ethyl group was transferred with a good level (entry 4). The reaction of **2d**, **2e**, and **2f** having an aromatic ring at R¹ gave a good degree of chirality transfer, whereas that of **1g** and **1h** bearing an alkyl group at the alkynyl moiety proceeded much more slowly and showed a decrease in the level of chirality transfer (entries 5–9). Particularly,

Scheme 1

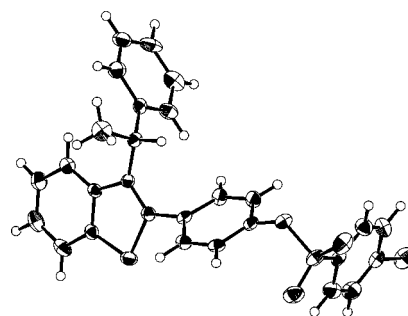
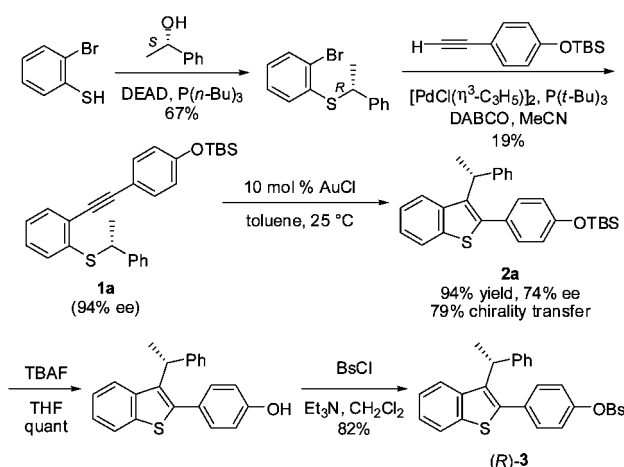
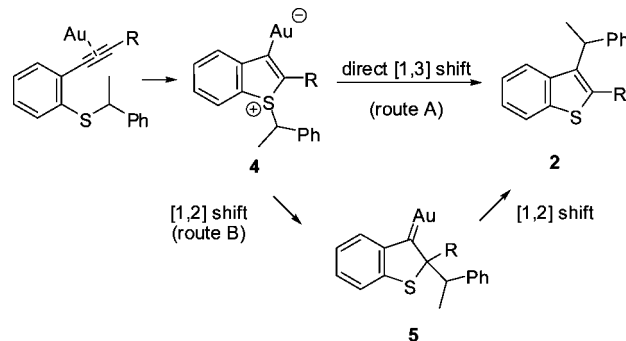


Figure 1. ORTEP drawing of (*R*)-**3**.

the reaction of **1h** having a bulky cyclohexyl group at R¹ took 5 days to complete with a poor chirality transfer (entry 9). In the reaction of **1h**, we observed in situ racemization of the starting material; when the reaction was quenched at 1 day, the product **2h** was obtained in 57% yield with 33% of chirality transfer along with 28% of the recovered **1h** of which the enantiomeric excess was 9%.

To know if the carbodemetalation process of the sulfonium intermediate **4** to give the product **2** proceeded through direct [1,3] shift of the α -phenethyl group (Scheme 2, route A) or

Scheme 2. Carbodemetalation Process in the Au-Catalyzed Carbothiolation



[1,2] migration of the α -phenethyl group forming the gold-carbenoid intermediate **5** followed by the second [1,2] migration (route B),⁷ we carried out the labeling experiment using the deuterated substrate **6** (eq 4). The reaction of **6** under the standard reaction conditions gave **7** in 89% yield; only a trace of the [1,2] shift-derived product **8** was observed in ¹H NMR spectroscopy. This result clearly indicates that the present reaction proceeds mainly through direct [1,3] migration of the α -phenethyl group.

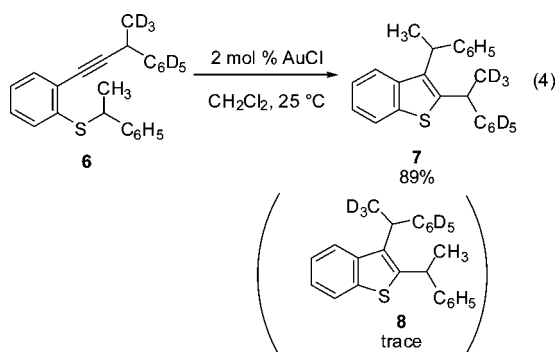
(6) CCDC-666893 contains the supplementary crystallographic data for **3**. The data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, U.K.; fax (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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Table 1. Chirality Transfer in Gold-Catalyzed Carbothiolation of *o*-Alkynylphenyl 1-Arylethyl Sulfides **1**^a

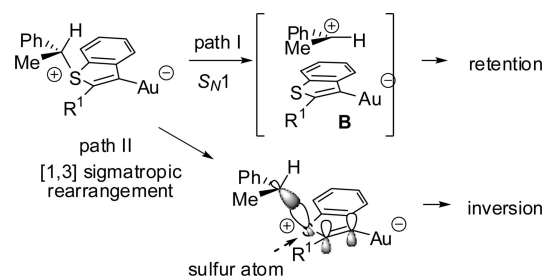
entry	1	R ¹	R ²	ee of 1 , % ^c	temp, °C	time, h	2	yield, % ^b	ee of 2 , % ^c	chirality transfer, %
1	1b	<i>p</i> -anisyl	Ph	97	25	0.5	2b	98	88	91
2	1b	<i>p</i> -anisyl	Ph	97	50	0.5	2b	99	79	52
3	1b	<i>p</i> -anisyl	Ph	97	0	4 days	2b	97	69	71
4	1c	<i>p</i> -anisyl	<i>p</i> -ClC ₆ H ₄	98	25	0.5	2c	97	79	81
5	1d	Ph	Ph	98	25	2	2d	quant	78	79
6	1e	<i>p</i> -F ₃ CC ₆ H ₄	Ph	95	25	2	2e	87	72	76
7	1f	6-methoxy-2-naphthyl	Ph	99	25	2	2f	93	82	82
8	1g	<i>n</i> -Pr	Ph	>99	25	3 days	2g	82	38	38
9	1h	cyclohexyl	Ph	>99	25	5 days	2h	92	22	23

^a The reaction of **1** (0.2 mmol) was carried out in the presence of 2 mol % of AuCl in 1 mL of CH₂Cl₂ at 25 °C. ^b Isolated yield. ^c Enantiomeric excess was determined by chiral HPLC analysis.



Retention of the stereocenter suggests that the [1,3] migration of α -phenethyl group in the present chirality transfer reaction proceeds through generation of the contact ion-pair **B** followed by C–C bond formation before racemization of the stereocenter (Scheme 3, path I).⁸ Decrease of the level of chirality transfer in the reaction of **1b** at 50 °C is probably because the separation of the ion-pair **B** occurs faster at higher temperature, resulting in higher degree of racemization (Table 1, entry 2). Obviously, an aryl group at R¹ plays an important role for rate acceleration (e.g., Table 1, entry 1 versus 8). Perhaps, interaction between the π -electron of the aromatic ring at R¹ and the α -phenethyl cation facilitates migration of the α -phenethyl group. Since the [1,3] sigmatropic rearrangement would proceed antarafacially with *inversion* of the stereocenter at the α -phenethyl group,⁹ the possibility of concerted [1,3] migration is illogical (path II).

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Scheme 3

In conclusion, we have found that the chirality transfer in the gold-catalyzed carbothiolation of **1** proceeds with retention of the stereocenter at α -phenethyl group. Further mechanistic investigations including chirality transfer in indole and benzofuran synthesis are on going in our laboratory.

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Supporting Information Available: Experimental procedures and characterization of the products **1**, **2**, **3**, **6**, and **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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