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

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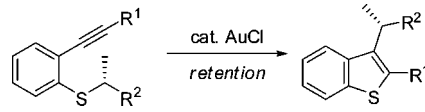
ABSTRACT



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.

(2) Migration of allyl groups: (a) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001–1011. (b) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025. (c) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181–3184. Propargyl groups: (d) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101–5104. Acyl groups: (e) Shimada; T.; Nakamura, I.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 10546–10547. Sulfonyl groups: (f) Nakamura, I.; Yamagishi, U.; Song, D.; Konta, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 2284–2287.

(3) Allyl groups: Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280–9288. (b) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741–745. (c) Monterio, N.; Balme, G. *Synlett* **1998**, 746–747. (d) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785–6786. (e) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869. α-Alkoxyalkyl groups: (f) Nakamura, I.; Mizushima, Y.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15022–15023. (g) Fürstner, A.; Heilmann, E. K.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 4760–4763.

(4) (a) Nakamura, I.; Sato, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 4473–4475. (b) Nakamura, I.; Sato, T.; Terada, M.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 4081–4083.

(5) Au-catalyzed chirality transfer reactions: (a) Hoffmann-Röder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537–2538. (b) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 15978–15979. (c) Nieto Faza, O.; Silva López, C.; Álvarez, R.; de Lera, A. R. *J. Am. Chem. Soc.* **2006**, *128*, 2434–2437. (d) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066–9073. (e) Dubé, P.; Toste, F. D. *J. Am. Chem. Soc.* **2006**, *128*, 12062–12063. (f) Nishina, N. Yamamoto, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 3314–3317.

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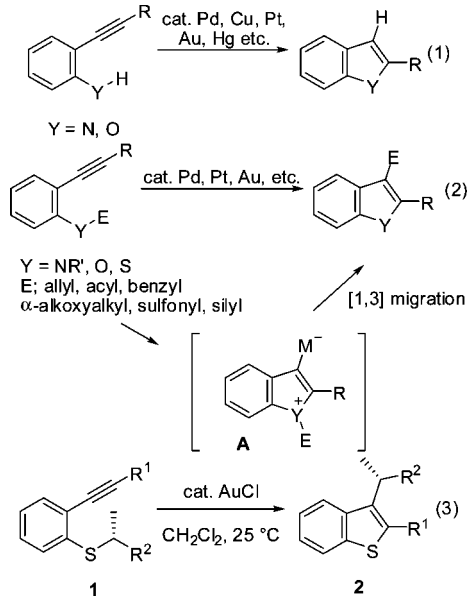
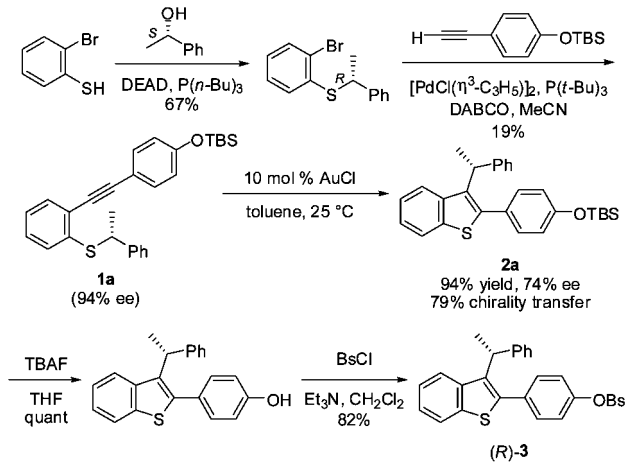


X-ray crystallographic analysis (Figure 1).[6] The present reaction is concluded to proceed with retention of the configuration at the α-phenethyl group.

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 (entry1). Among the solvents we examined, we found that the use of CH_2Cl_2 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 R^1 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



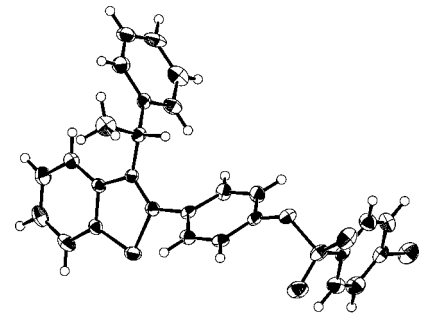
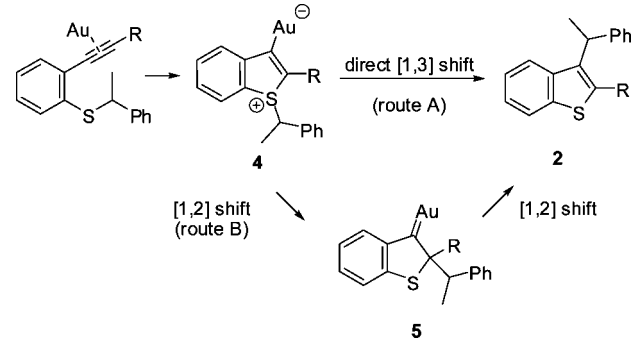


Figure 1. ORTEP drawing of (*R*)-**3**.

the reaction of **1h** having a bulky cyclohexyl group at R^1 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 enatiomeric 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 ^{1}H NMR spectroscopy. This result clearly indicates that the present reaction proceeds mainly through direct [1,3] migration of the α-phenethyl group.

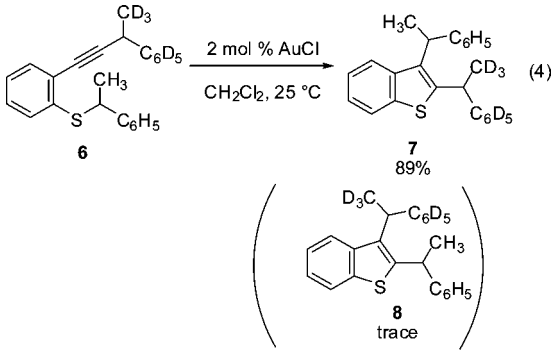
(6) CCDC-666893 contains the supplementary crystallographic data for **3**. The data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, U.K.; fax (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

(7) (a) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289–292. (b) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int.Ed.* **2008**, *47*, 346–349.

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

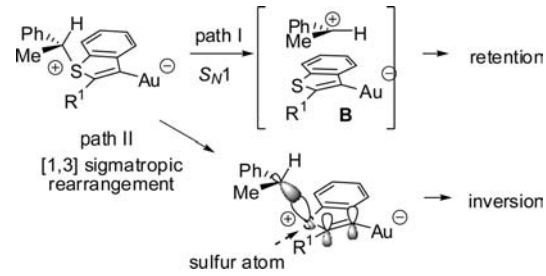
entry	1	R^1	R^2	ee of 1, %[c]	temp, °C	time, h	2	yield, %[b]	ee of 2, %[c]	chirality transfer,%
1	**1b**	*p*-anisyl	Ph	97	25	0.5	**2b**	98	88	91
2	**1b**	*p*-anisyl	Ph	97	50	0.5	**2b**	99	79	52
3	**1b**	*p*-anisyl	Ph	97	0	4 days	**2b**	97	69	71
4	**1c**	*p*-anisyl	*p*-ClC_6H_4	98	25	0.5	**2c**	97	79	81
5	**1d**	Ph	Ph	98	25	2	**2d**	quant	78	79
6	**1e**	*p*-$F_3CC_6H_4$	Ph	95	25	2	**2e**	87	72	76
7	**1f**	6-methoxy-2-naphthyl	Ph	99	25	2	**2f**	93	82	82
8	**1g**	*n*-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 CH_2Cl_2 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 R^1 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 R^1 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).

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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(8) (a) Kawabata, T.; Fuji, K. *Top. Stereochem.* **2003**, *23*, 175–205. (b) Goering, H. L.; Levy, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 120–121. (c) Decoret, C.; Royer, J.; Dannenberg, J. J. *J. Org. Chem.* **1981**, *46*, 4074–4076.

(9) March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992; pp 1126.