Pergamon

Tetrahedron: *Asymmetry* 10 (1999) 2511–2514

TETRAHEDRON: *ASYMMETRY*

Palladium(0) catalyzed enantioselective rearrangement of *O*-allylic thiocarbamates to *S*-allylic thiocarbamates: asymmetric synthesis of allylic thiols

Achim Böhme and Hans-Joachim Gais *

Institut für Organische Chemie der Rheinisch-Westfälischen Technischen Hochschule Aachen, Professor-Pirlet-Straße 1, D-52056 Aachen, Germany

Received 1 June 1999; accepted 23 June 1999

Abstract

The Pd(0) catalyzed rearrangement of the *O*-allylic thiocarbamates *rac*-**2a**, *rac*-**2b** and *rac*-**4** in the presence of the chiral bisphosphane **5** proceeded quantitatively and gave the *S*-allylic thiocarbamates **6a**, **6b** and **7**, respectively, with 91, 92 and 97% ee, respectively, in high yields. Saponification of the *S*-allylic thiocarbamate **7** furnished the allylic thiol **9** with 97% ee.

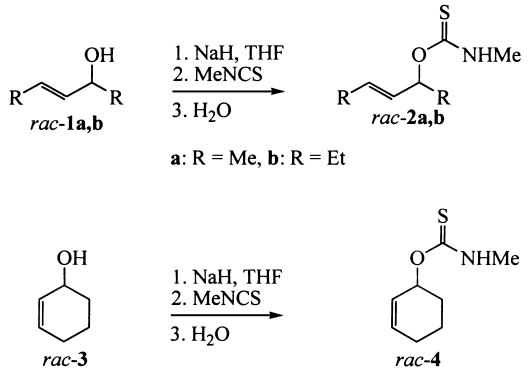
The Pd(0) catalyzed allylic alkylation of sulfinates in the presence of chiral phosphanes provides an effective means for the asymmetric synthesis of allylic aryl as well as alkyl sulfones.[1–6] We have recently described the utilization of this method for the asymmetric synthesis of allylic heteroaryl sulfides from the corresponding thiols.[7] Unfortunately, however, all attempts to extend the Pd(0) catalyzed allylation to alkyl thiols were unsuccessful. The low reactivity of alkyl thiols in the Pd(0) catalyzed allylic alkylation seems to be a general phenomenon.[8–15] Because of the ready alkylation,[16,17] arylation,[18–20] heteroarylation (vide infra),[16,17] and further functionalization of thiols at the *S*-atom,[16,17] chiral allylic thiols would be ideal starting materials for the synthesis of a broad range of chiral allylic sulfides provided that an asymmetric synthesis of the former were available. The results of previous studies of the Pd(0)/PPh_3 catalyzed rearrangement of *O*-allylic phosphorothionates,[21] phosphonothionates,[21] thioesters[9,10] and thiocarbamates[18] suggested a perhaps facile asymmetric synthesis of allylic thiols by using as the key step an enantioselective Pd(0) catalyzed rearrangement of racemic *O*-allylic phosphorothionates, phosphonothionates, thioesters, or thiocarbamates to the corresponding enantiomerically enriched *S*-allylic isomers.

Herein, we describe the successful realization of this concept in the case of *O*-allylic thiocarbamates having a symmetrical carbon skeleton.

* Corresponding author. E-mail: gais@rwth-aachen.de

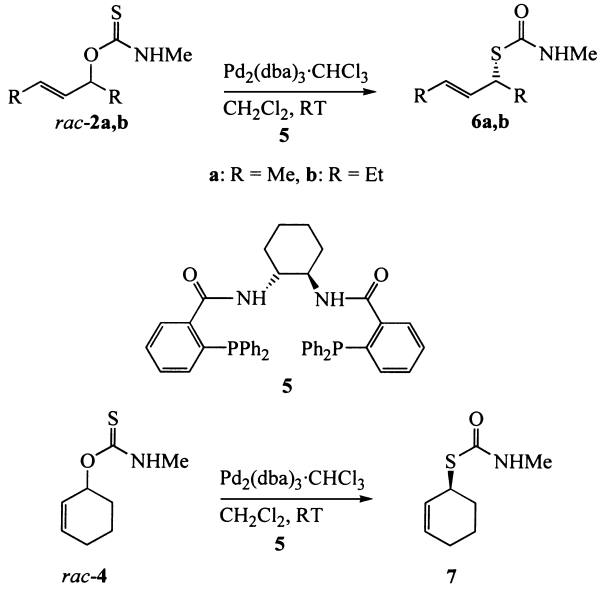
0957-4166/99/$ - see front matter
PII: S0957-4166(99)00263-3

The racemic *O*-allylic thiocarbamates *rac*-**2a**, *rac*-**2b** and *rac*-**4** were synthesized in nonoptimized yields of 73, 51 and 66%, respectively, from the racemic allylic alcohols *rac*-**1a**, *rac*-**1b** and *rac*-**3**, respectively, and methyl isothiocyanate[18] (Scheme 1).



Scheme 1.

Because of the high enantioselectivities recorded in the Pd(0) catalyzed allylic substitution of the racemic carbonates derived from *rac*-**1a**, *rac*-**1b** and *rac*-**3** with heteroaromatic thiols and sulfinates by using the bisphosphane **5**,[2–7] we have chosen this ligand for the Pd(0) catalyzed rearrangement of *rac*-**2a**, *rac*-**2b** and *rac*-**4** (Scheme 2). Treatment of the *O*-allylic thiocarbamate *rac*-**2a** with $Pd_2(dba)_3 \cdot CHCl_3$ (dba=dibenzylideneacetone) and **5** in methylene chloride at room temperature led to a quantitative rearrangement and gave the *S*-allylic thiocarbamate **6a** with an ee-value of 91% in 92% yield (Table 1, entry 1). The rearrangement of *rac*-**2b** under the same conditions furnished **6b** with 92% ee in 94% yield (Table 1, entry 2).



Scheme 2.

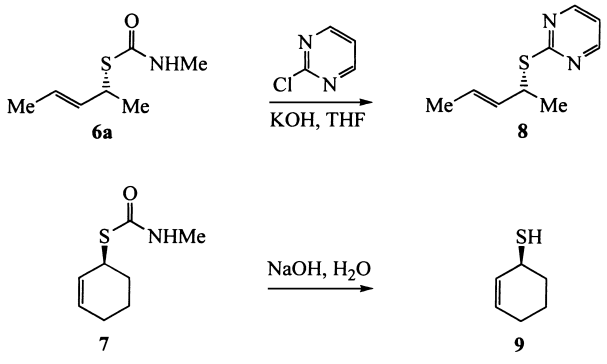
This highly enantioselective rearrangement is not restricted to acyclic substrates. Treatment of the cyclic thiocarbamate *rac*-**4** with $Pd_2(dba)_3 \cdot CHCl_3$ and **5** in methylene chloride after a reaction time of 3 h at room temperature delivered the *S*-allylic thiocarbamate **7** with an ee-value of 97% in 94% yield

Table 1
Pd(0) catalyzed rearrangement of *O*-allylic thiocarbamates

entry	substrate	Pd/**5** (mol %)	time (h)	product	conv. (%)	yield (%)	ee (%)	$[\alpha]_D^{20}$ ($CHCl_3$)
1	*rac*-**2a**	2.5/3	15	**6a**	100	92	91	+97.4 (*c*, 13.6)
2	*rac*-**2b**	7.5/9	15	**6b**	100	94	92	+84.4 (*c*, 11.1)
3	*rac*-**4**	1.25/1.5	3	**7**	100	94	97	–226.0 (*c*, 10.9)

(Table 1, entry 3). In the case of *rac*-**4** the rearrangement could be accomplished by using 1.25 mol% of Pd and 1.5 mol% of **5**.

The ee-values of **6a**, **6b** and **7** were determined by GC analysis on an octakis-(2,6-di-*O*-pentyl-3-*O*-butyryl)-ɣ-cyclodextrin column [*rac*-**6a**: t_R (**6a**)=48.9 min, t_R (*ent*-**6a**)=48.8 min; *rac*-**6b**: t_R (**6b**)=50.1 min, t_R (*ent*-**6b**)=49.9 min] and on an octakis-(2,3-*O*-dipentyl-6-*O*-methyl)-ɣ-cyclodextrin column [*rac*-**7**: t_R (**7**)=103.3 min, t_R (*ent*-**7**)=103.2 min]. Determination of the absolute configuration of **6a** was made by chemical correlation with the sulfide (+)-(*R*)-**8**[7] of known absolute configuration (Scheme 3). Thus, (+)-**6a** was treated with 2-chloropyrimidine in the presence of potassium hydroxide in THF at reflux to give (+)-**8** in 95% yield. Since **6a** and **6b** have the same sign of optical rotation the (*R*) configuration was also assigned to **6b**.



Scheme 3.

The feasibility of the synthesis of enantiomerically highly enriched allylic thiols from the corresponding *S*-allylic thiocarbamates under basic conditions was demonstrated by the saponification of **7** with sodium hydroxide in aqueous solution which furnished the allylic thiol **9**,[22] having the (*S*) configuration, with 97% ee $[\alpha]_D^{20}$ −271.3 (*c* 0.8, $CHCl_3$)) in a nonoptimized yield of 63%. The ee-value of **9** was determined by GC analysis on an octakis-(2,6-di-*O*-pentyl-3-*O*-butyryl)-ɣ-cyclodextrin column [t_R (**9**)=6.7 min, t_R (*ent*-**9**)=6.5 min]. The above-described Pd(0) catalyzed enantioselective synthesis of allylic thiols is synthetically especially attractive because it uses racemic allylic alcohols as the starting materials and renders the use of an external nucleophile superfluous. In the cases investigated the thermal rearrangement of the *O*-allylic thiocarbamates[18] posed no problem.

The stereochemical course of the Pd(0) catalyzed rearrangement of *rac*-**2a**, *rac*-**2b** and *rac*-**4** in the presence of the bisphosphane **5** is the same as observed in the case of the Pd(0) catalyzed allylic substitution of the carbonates of *rac*-**1a**, *rac*-**1b** and *rac*-**3** with heteroaromatic thiols and sulfinates by using this ligand. This observation in combination with the results of previous mechanistic studies of the Pd(0)/PPh_3 catalyzed rearrangement of *O*-allylic thiocarbamates[18] suggests that **6a**, **6b** and **7** are formed

by an external attack of the nucleophile *N*-methyl thiocarbamate on the corresponding chiral Pd(II)-π-allylic complexes derived from *rac*-**2a**, *rac*-**2b** and *rac*-**4**, respectively.[23]

Acknowledgements

Financial support of this work by the Deutsche Forschungsgemeinschaft (SFB 380) is gratefully acknowledged.

References

1. Eichelmann, H.; Gais, H.-J. *Tetrahedron: Asymmetry* **1995**, *6*, 643–646.
2. Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc*. **1995**, *117*, 9662–9670.
3. Trost, B. M.; Krische, M. J.; Radinov, R.; Zanoni, G. *J. Am. Chem. Soc*. **1996**, *118*, 6297–6298.
4. Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc*. **1996**, *118*, 6520–6521.
5. Trost, B. M.; Radinov, R. *J. Am. Chem. Soc*. **1997**, *119*, 5962–5963.
6. Gais, H.-J.; Eichelmann, H.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Tetrahedron: Asymmetry* **1998**, *9*, 235–248.
7. Frank, M.; Gais, H.-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3353–3357.
8. Trost, B. M.; Scanlan, T. S. *Tetrahedron Lett*. **1986**, *27*, 4141–4144.
9. Auburn, P. R.; Whelan, J.; Bosnich, B. *J. Chem. Soc., Chem. Commun*. **1986**, 146–147.
10. Auburn, P. R.; Whelan, J.; Bosnich, B. *Organometallics* **1986**, *5*, 1533–1537.
11. Goux, C.; Lhoste, P.; Sinou, S. *Tetrahedron Lett*. **1992**, *33*, 8099–8102.
12. Moreno-Mañas, M.; Pleixats, R.; Villarroya, M. *Tetrahedron* **1993**, *49*, 1457–1464.
13. Arredono, Y.; Moreno-Mañas, M.; Pleixats, R.; Villarroya, M. *Tetrahedron* **1993**, *49*, 1465–1470.
14. Goux, C.; Lhoste, P.; Sinou, S. *Tetrahedron* **1994**, *33*, 10321–10330.
15. Divekar, S.; Safi, M.; Soufiaoui, M.; Sinou, D. *Tetrahedron* **1999**, *55*, 4369–4376.
16. Gundermann, K.-D.; Hümke, K. In *Organische Schwefel-Verbindungen (Houben-Weyl)*; Klamann, D., Ed.; Thieme: Stuttgart, 1985; Vol. E11, pp. 158–187.
17. Page, P. C. B.; Wilkes, R. D.; Reynolds, D. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R.; Meth-Cohn, O.; Rees, C. W.; Ley, S. V., Eds.; Pergamon: Oxford, 1995; Vol. 2, pp. 113–275.
18. Harayama, H.; Nagahama, T.; Kozera, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *Bull. Chem. Soc. Jpn*. **1997**, *70*, 445–456.
19. Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc*. **1998**, *120*, 9205–9219.
20. Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong III, J. D.; Volante, R. P. *J. Org. Chem*. **1998**, *63*, 9606–9607.
21. Tamaru, Y.; Yoshida, Z.; Yamada, Y.; Mukai, K.; Yoshioka, H. *J. Org. Chem*. **1983**, *48*, 1293–1297.
22. Ernst, B.; Gonda, J.; Jeschke, R.; Nubbemeyer, U.; Oehrlein, R.; Bellus, D. *Helv. Chim. Acta* **1997**, *80*, 876–891.
23. Compounds *rac*-**2a**, *rac*-**2b**, *rac*-**4**, **6a**, **6b**, **7**, and **9** have been fully characterized by NMR, MS and elemental analysis.