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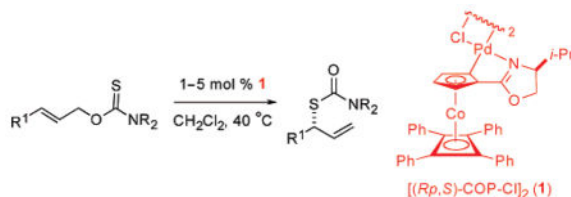
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Catalytic Asymmetric Synthesis of Allylic Thiol Derivatives

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Abstract



The palladium(II) complex $[(R_p,S)\text{-COP-Cl}]_2$ and its enantiomer catalyze the rearrangement of linear prochiral *O*-allyl carbamothioates under mild conditions to provide branched *S*-allyl carbamothioates in high yield and high enantiomeric purity.

Catalytic methods for enantioselective construction of C–S bonds are less well developed than those for forming C–C, C–O, and C–N linkages. Among the most powerful methods are enantioselective palladium(0)-catalyzed displacements of allylic ester or carbonate precursors with sulfinate, thiolate, and thiocarboxylate nucleophiles and mechanistically related rearrangements of *O*-allyl sulfonates and carbamothioates.^{1–3} However, these methods are only useful for accessing products derived from symmetrically substituted η^3 -allylpalladium precursors because of low regioselectivity in the capture of unsymmetrical η^3 -allylpalladium intermediates by sulfur nucleophiles.^{2c,3}

The formation of allylic sulfur compounds by [3,3]-sigmatropic rearrangements of allylic thiocarbonyl compounds, promoted thermally⁴ or by metal-catalyzed cyclization-induced rearrangement mechanisms,^{5,6} typically is not complicated by issues of regioselectivity. However, to date, catalytic enantioselective variants of such rearrangements have not been reported. Herein, we disclose that the commercially available palladium(II) complex $[(R_p,S)\text{-COP-Cl}]_2$ (**1**)⁷ and its enantiomer catalyze the rearrangement of linear prochiral *O*-allyl carbamothioates to provide branched *S*-allyl carbamothioates in high yield and high enantiomeric purity, products that are readily transformed to the parent allylic thiols.^{3c,d}

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Supporting Information Available: Experimental procedures; characterization data for new compounds (¹H, ¹³C, and HMQC NMR spectra); copies of SFC, GC, and HPLC traces used to establish the enantiopurity of (*E*)-*S*-allylic carbamothioate products; and details of chemical correlations to establish absolute configuration of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Because of the success of palladium(II) complexes of the COP family for catalyzing enantioselective [3,3]-sigmatropic rearrangements of prochiral allylic imidates to allylic amides,⁸ we examined the complexes depicted in Figure 1 as catalysts for the rearrangement of (*E*)- and (*Z*)-*O*-2-hexenyl methylxanthates **6** and **7** (Table 1).^{7,9} Chloride-bridged dimer [(*Rp,S*)-COP-Cl]₂ (**1**) proved to be the most effective catalyst. With a catalyst loading of 1 mol %, *S*-methylcarbonodithioate **8** was formed in 66% ee and 90% conversion after 20 h at 40 °C from *E* precursor **6** (entry 1).¹⁰ As expected for a cyclization-induced rearrangement,^{8d} the *Z* stereoisomer rearranged more slowly (entries 6–10).¹¹ Again, COP complex **1** was the best of the catalysts surveyed in terms of both reaction rate and enantioselection (entry 6).

To further optimize enantioselection, the nature of the thiocarbonyl substituent was varied. A series of (*E*)-*O*-2-hexenyl carbamothioates were prepared from (*E*)-2-hexenol (**9**),^{12,13} and their rearrangement in the presence of 1 mol % of [(*Rp,S*)-COP-Cl]₂ at 40 °C in CH₂Cl₂ was examined (Table 2). Although no trend in reaction rate was apparent, enantioselectivity was highest in the rearrangements of *O*-carbamothioates containing the smallest nitrogen substituents: dimethylamino (**10a**) and 1-azetidynyl (**10c**) (entries 1 and 3). Subjecting of **10a** and **10c** to the same reaction conditions in the absence of catalyst resulted in recovery of starting material, establishing that the thermal rearrangement of these substrates was negligible under these conditions.¹⁴

Having determined that *O*-allyl carbamothioates having dimethylamino or 1-azetynyl substituents rearranged with higher enantioselectivity, we turned our attention to developing an optimized general procedure for the [COP-Cl]₂-catalyzed rearrangement of *O*-allyl methyl- and 1-azetynyl-carbamothioates. As expected, increasing the catalyst loading from 1 to 5 mol % significantly reduced reaction times. However, the higher catalyst loadings complicated the purification of the transposed allyl *S*-carbamothioates, with traces of COP complexes contaminating the product. Simply adding ethylenediamine (0.5 equiv) to the crude reaction solution at the conclusion of the reaction¹⁵ allowed pure products to be isolated reproducibly in high yields.^{16,17}

Using this optimized procedure, the catalytic asymmetric rearrangement of various *O*-allyl dimethyl- and 1-azetidynylcarbamothioates was surveyed (Table 3). The starting 1-azetidynecarbamothioates **10c** and **12** were prepared in good overall yields (54–97%) from (*E*)-allylic alcohol precursors by reaction of *O*-methylxanthate intermediates with azetidine hydrochloride and triethylamine at room temperature.¹⁸ *O*-Allyl dimethylcarbamothioates **10a** and **13** were prepared in one step and high yields by the reaction of dimethylthiocarbonyl chloride with the appropriate allylic alcohol.¹⁸ Yields of the branched *S*-allyl carbamothioate products were generally excellent (85–99%). Two exceptions were products **14e** and **14f** that contain hydroxyl and Boc-protected aniline substituents, which were formed in lower yields (55–77% yield) (entries 8–10). Products containing linear or branched hydrocarbon substituents (entries 1–3), or homoallylic TBDMS- and TIPS-protected alcohol substituents (entries 3–6), were obtained in high enantiomeric purities (80–88% ee). Enantioselectivity was somewhat reduced in rearrangements of substrates containing unprotected allylic alcohol or a keto substituent at C5 (entries 8 and 11). Carrying out the rearrangement reported in entry 1 with the [(*Sp,R*)-COP-Cl]₂ (*ent*-**1**) provided

ent-**11c** in 83% ee and 98% yield. Although the reaction time was longer (67 h), the rearrangement of **10c** (entry 1) with *ent*-**1** could be readily carried out at room temperature, giving *ent*-**11c** in 82% ee and 96% yield. The catalyst loading could be reduced to 1 mol %, although the reaction had to be run for a longer time. For example, carrying out the rearrangement reported in entry 1 for 47 h at 40 °C at 1 mol % catalyst loading provided **11c** in 76% ee and 95% yield. Absolute configurations of **11a–e** were determined by chemical correlation with (*R*)-*S*-hex-1-yn-3-yl benzothioate, which was prepared by Mitsunobu reaction of (*S*)-hex-1-yn-3-ol with *S*-benzothioic acid.^{18,19} The absolute configuration of other *S*-allyl carbamothioates products was assigned by analogy.

In summary, a new catalytic asymmetric method for preparing allylic thiol derivatives has been developed. It is the first catalytic asymmetric method that provides branched allylic thiol derivatives in high regioselectivity from prochiral linear allylic precursors. Attractive features of the method include the ready synthesis of (*E*)-*S*-allyl carbamothioates from allylic alcohol precursors, the high yields and good enantioselection observed in their catalytic asymmetric rearrangement with [COP-Cl]₂, and the ability to transform the branched allyl *S*-carbamothioate product to the corresponding enantioenriched branched allylic thiol by reduction with lithium aluminum hydride.^{3c,d,18}

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 9. The preparation and characterization of COP complexes **3** and **5** will be described in a forthcoming publication.
 10. The half-life of the thermal background reaction is ~60 h under these conditions, which likely contributed somewhat to lowering enantioselection.
 11. The thermal background reaction for rearrangement of (*Z*)-*O*-2-hexenyl methylxanthate **7** was negligible.
 12. *O*-Hexenyl carbamothioate **10a** was prepared by reaction of alcohol **9** with commercially available dimethylthiocarbamoyl chloride, whereas substrates **10b–e** were prepared by reaction of (*E*)-*O*-2-hexenyl methyl xanthate **6** with the corresponding secondary amine. Details can be found in the Supporting Information.
 13. Barrett AGM, Prokopiou PA, Barton DHR. *J Chem Soc, Perkin Trans.* 1981; 1:1510–1515.
 14. The (*E*)-*O*-2-hexenyl carbamothioate containing an NHPH substituent, prepared from the reaction of allylic alcohol **9** with phenyl isothiocyanate, rearranged in low enantioselectivity. The *O*-benzothioate derivative of **9** rearranged with good enantioselectivity; however, its relative instability led to low yields of the product, *S*-hex-1-en-3-yl benzothioate.
 15. Urawa Y, Miyazawa M, Ozeki N, Ogura K. *Org Process Res Dev.* 2003; 7:191–195.
 16. Adding polymer-supported ethylenediamine, followed by filtration, was initially attempted. However, the product still contained ~5% of a palladium impurity.
 17. Many literature reports address the removal of palladium residues from reaction mixtures. See inter alia: Larsen RD, King AO, Chen CY, Corley EG, Foster BS, Roberts FE, Yang C, Lieberman DR, Reamer RA, Tschaen DM, Verhoeven TR, Reider PJ, Lo YS, Rossano LT, Brookes AS, Meloni D, Moore JR, Arnett JF. *J Org Chem.* 1994; 59:6391–6394. Rosso VW, Lust DA, Bernot PJ, Grosso JA, Modi SP, Rusowicz A, Sedergran TC, Simpson JH, Srivastava SK, Humora MJ, Anderson NG. *Org Process Res Dev.* 1997; 1:311–314. Chen C, Dagneau P, Grabowski EJJ, Oballa R, O'Shea P, Prasit P, Robichaud J, Tillyer R, Wang X. *J Org Chem.* 2003; 68:2633–2638. [PubMed: 12662032]
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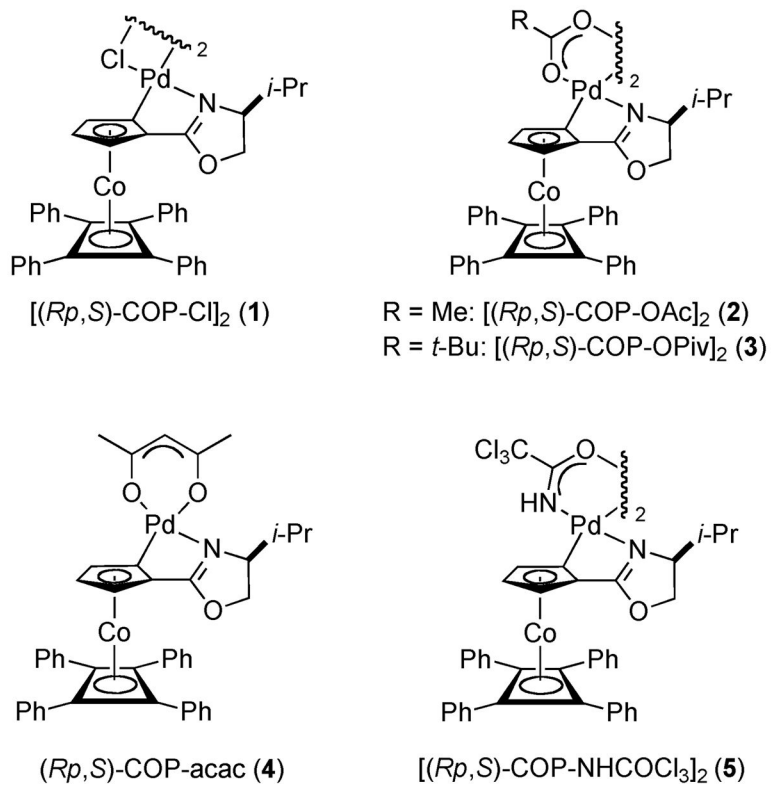
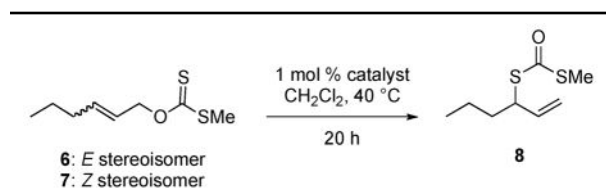


Figure 1.
COP palladium(II) catalysts.

Table 1

Performance of Various Palladium(II) COP Catalysts in the Enantioselective Rearrangement of *O*-2-Hexenyl Methylxanthates **6** and **7**



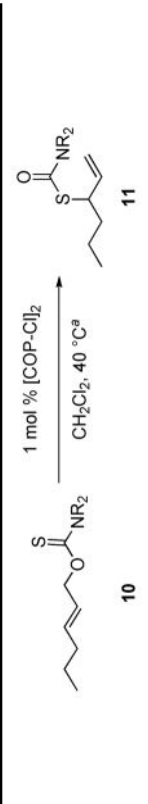
entry	xanthate ^a	catalyst	convn. % ^b	ee % ^c
1	6	[COP-Cl] ₂ (1)	90	66
2	6	COP-acac (4)	75	50
3	6	[COP-OPiv] ₂ (3)	42	31
4	6	[COP-OAc] ₂ (2)	45	30
5	6	[COP-NHCOCl ₃] ₂ (5)	35	10
6	7	[COP-Cl] ₂ (1)	27	50
7	7	[COP-OPiv] ₂ (3)	14	49
8	7	[COP-OAc] ₂ (2)	14	35
9	7	COP-acac (4)	12	10
10	7	[COP-NHCOCl ₃] ₂ (5)	5	6

^aSubstrate concentration = 0.25 M.

^bAt 20 h, by GC analysis.

^cDetermined by HPLC analysis using a chiral stationary phase.

Table 2

[COP-Cl]₂-Catalyzed Rearrangements of (*E*)-*O*-2-Hexenyl Carbamothioates **10**


entry	R ₂	catalyst abs. conf.	compd	product	
				yield % ^b	ee % ^c (abs. conf.) ^d
1	Me ₂ (10a)	<i>Sp,R</i>	11a	72	82 ^e (<i>R</i>)
2	Et ₂ (10b)	<i>Sp,R</i>	11b	78	59 ^f (<i>R</i>)
3	1-azetiny1 (10c)	<i>Sp,R</i>	11c	98	83 (<i>R</i>)
4	1-pyrrolidiny1 (10d)	<i>Rp,S</i>	11d	100	57 (<i>S</i>)
5	1-piperidiny1 (10e)	<i>Rp,S</i>	11e	71	76 ^f (<i>S</i>)

^aSubstrate concentration = 0.2–0.5 M.^bYield of product after purification by column chromatography.^cDetermined by HPLC or SFC analysis using a chiral stationary phase.^dSee the Supporting Information for determination of absolute configuration.^eDetermined by GC analysis using a chiral stationary phase.^fThe corresponding *S*-benzothioates prepared from **11b** and **11e** were analyzed (see the Supporting Information).

Table 3

Scope of the [(*Rp,S*)-COP-Cl]₂-Catalyzed Rearrangement of (*E*)-*O*-Allyl Carbamothioates

entry	R ¹	R ₂	time, h ^c	compd	product	
					yield % ^d	ee % ^e
1 ^b	<i>n</i> -Pr	1-azetinylyl	15	<i>ent</i> - 11c	98	83
2 ^b	<i>n</i> -Pr	Me ₂	18	<i>ent</i> - 11a	72	82
3	CH ₂ CH(CH ₃) ₂	1-azetinylyl	42	14a	85	80
4	CH ₂ OTBDMS	1-azetinylyl	20	14b	85	88
5	CH ₂ OTBDMS	Me ₂	18	15a	97	87 ^{f,g}
6	CH ₂ OTIPS	1-azetinylyl	42	14c	99	87 ^f
7	CH ₂ OTBDPS	1-azetinylyl	42	14d	86	76 ^f
8	CH ₂ OH	1-azetinylyl	13	14e	55	61
9	CH ₂ NPh(Boc)	1-azetinylyl	44	14f	68	71
10	CH ₂ NPh(Boc)	Me ₂	43	15b	77	81
11	(CH ₃) ₂ COMe	1-azetinylyl	11	14g	85	76

^aSubstrate concentration = 0.5 M.^b*Sp,R* enantiomer of [COP-Cl]₂ was used.^cTime for disappearance of starting material by TLC analysis.^dYield of product after purification by column chromatography.^eDetermined by SFC analysis using a chiral stationary phase; results from duplicate experiments agreed within ± 1%.^fDetermined after conversion of the product to alcohol **14e**.^gDetermined by GC analysis using a chiral stationary phase; results from duplicate experiments agreed within ±2%.