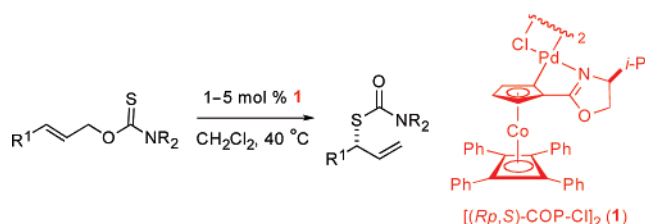


Catalytic Asymmetric Synthesis of  
Allylic Thiol DerivativesLarry E. Overman,\* Scott W. Roberts, and Helen F. Sneddon<sup>§</sup>Department of Chemistry, 1102 Natural Sciences II, University of California,  
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## ABSTRACT



The palladium(II) complex [(*Rp,S*)-COP-Cl]<sub>2</sub> 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.<sup>1–3</sup> However, these methods are only useful for accessing products derived from symmetrically substituted  $\eta^3$ -allylpalladium precursors because of low regioselectivity in the capture of unsymmetrical  $\eta^3$ -allylpalladium intermediates by sulfur nucleophiles.<sup>2c,3</sup>

The formation of allylic sulfur compounds by [3,3]-sigmatropic rearrangements of allylic thiocarbonyl com-

pounds, promoted thermally<sup>4</sup> or by metal-catalyzed cyclization-induced rearrangement mechanisms,<sup>5,6</sup> 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 [(*Rp,S*)-COP-Cl]<sub>2</sub> (**1**)<sup>7</sup> 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.<sup>3c,d</sup>

Because of the success of palladium(II) complexes of the COP family for catalyzing enantioselective [3,3]-sigmatropic

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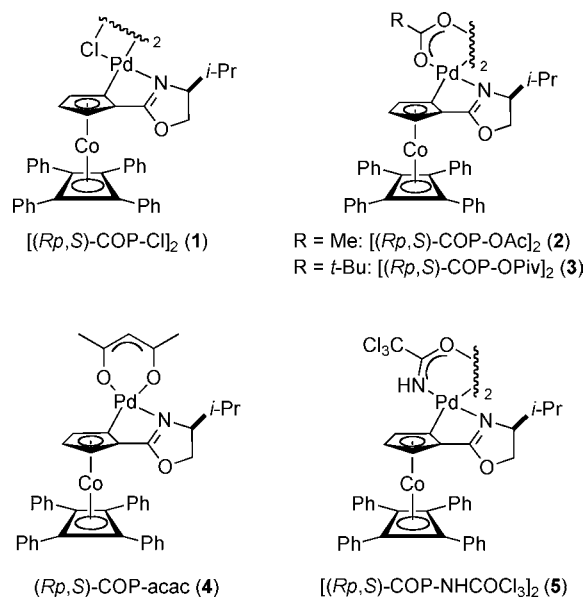
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**Figure 1.** COP palladium(II) catalysts.

rearrangements of prochiral allylic imidates to allylic amides,<sup>8</sup> 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).<sup>7,9</sup> Chloride-bridged dimer [(*Rp,S*)-COP-Cl]<sub>2</sub> (**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).<sup>10</sup> As expected for a cyclization-induced rearrangement,<sup>8d</sup> the *Z* stereoisomer rearranged more slowly (entries 6–10).<sup>11</sup> 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**),<sup>12,13</sup> and their rearrangement in the presence of 1 mol % of [(*Rp,S*)-COP-Cl]<sub>2</sub> at 40 °C in CH<sub>2</sub>Cl<sub>2</sub> was examined (Table 2). Although no trend in reaction rate was apparent, enantioselectivity was highest in the rearrangements of *O*-

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(9) The preparation and characterization of COP complexes **3** and **5** will be described in a forthcoming publication.

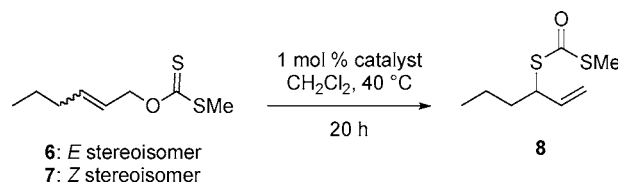
(10) The half-life of the thermal background reaction is ~60 h under these conditions, which likely contributed somewhat to lowering enantioselection.

(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 dimethylthiocarbonyl 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.

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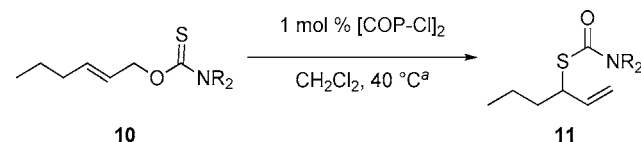
**Table 1.** Performance of Various Palladium(II) COP Catalysts in the Enantioselective Rearrangement of *O*-2-Hexenyl Methylxanthates **6** and **7**



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

<sup>a</sup>Substrate concentration = 0.25 M. <sup>b</sup>At 20 h, by GC analysis. <sup>c</sup>Determined by HPLC analysis using a chiral stationary phase.

**Table 2.** [COP-Cl]<sub>2</sub>-Catalyzed Rearrangements of (*E*)-*O*-2-Hexenyl Carbamothioates **10**



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

<sup>a</sup>Substrate concentration = 0.2–0.5 M. <sup>b</sup>Yield of product after purification by column chromatography. <sup>c</sup>Determined by HPLC or SFC analysis using a chiral stationary phase. <sup>d</sup>See the Supporting Information for determination of absolute configuration. <sup>e</sup>Determined by GC analysis using a chiral stationary phase. <sup>f</sup>The corresponding *S*-benzothioates prepared from **11b** and **11e** were analyzed (see the Supporting Information).

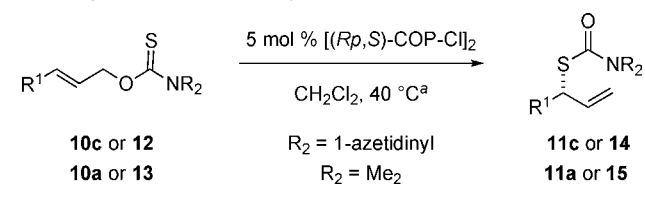
carbamothioates containing the smallest nitrogen substituents: dimethylamino (**10a**) and 1-azetidiny (**10c**) (entries 1 and 3). Subjection of **10a** and **10c** to the same reaction conditions in the absence of catalyst resulted in recovery of starting material, establishing that the thermal rearrangement of these substrates was negligible under these conditions.<sup>14</sup>

(14) The (*E*)-*O*-2-hexenyl carbamothioate containing an NPh 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.

Having determined that *O*-allyl carbamothioates having dimethylamino or 1-azetidinyl substituents rearranged with higher enantioselectivity, we turned our attention to developing an optimized general procedure for the [COP-Cl]<sub>2</sub>-catalyzed rearrangement of *O*-allyl methyl- and 1-azetidinyl-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 reaction<sup>15</sup> allowed pure products to be isolated reproducibly in high yields.<sup>16,17</sup>

Using this optimized procedure, the catalytic asymmetric rearrangement of various *O*-allyl dimethyl- and 1-azetidyl-carbamothioates was surveyed (Table 3). The starting

**Table 3.** Scope of the [(*Rp,S*)-COP-Cl]<sub>2</sub>-Catalyzed Rearrangement of (*E*)-*O*-Allyl Carbamothioates



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

<sup>a</sup> Substrate concentration = 0.5 M. <sup>b</sup> *Sp,R* enantiomer of [COP-Cl]<sub>2</sub> was used. <sup>c</sup> Time for disappearance of starting material by TLC analysis. <sup>d</sup> Yield of product after purification by column chromatography. <sup>e</sup> Determined by SFC analysis using a chiral stationary phase; results from duplicate experiments agreed within ±1%. <sup>f</sup> Determined after conversion of the product to alcohol **14e**. <sup>g</sup> Determined by GC analysis using a chiral stationary phase; results from duplicate experiments agreed within ±2%.

1-azetidyl-carbamothioates **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.<sup>18</sup> *O*-Allyl dimethylcarbamothioates **10a** and **13** were prepared

(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.

in one step and high yields by the reaction of dimethylthiocarbamoyl chloride with the appropriate allylic alcohol.<sup>18</sup> 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]<sub>2</sub> (*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.<sup>18,19</sup> 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]<sub>2</sub>, and the ability to transform the branched allyl *S*-carbamothioate product to the corresponding enantioenriched branched allylic thiol by reduction with lithium aluminum hydride.<sup>3c,d,18</sup>

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(18) See the Supporting Information for details.

(19) Corey, E. J.; Cimprich, K. A. *Tetrahedron Lett.* **1992**, *33*, 4099–4102.

and NIH Shared Instrumentation Programs. We thank Nicole White (UCI) and Professor Neil Garg (UCLA) for assistance with SFC analysis.

**Supporting Information Available:** Experimental procedures; characterization data for new compounds ( $^1\text{H}$ ,  $^{13}\text{C}$ , 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>.

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