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Phosphine-Catalyzed Formation of Carbon−Sulfur Bonds: Catalytic Asymmetric Synthesis of γ-Thioesters

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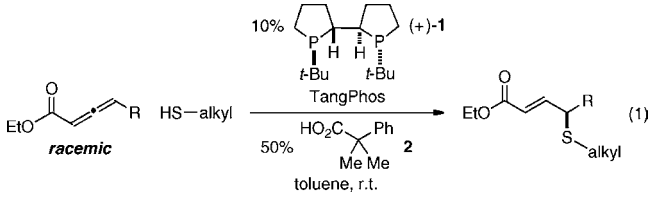
Chiral sulfur-containing compounds have important applications in many areas of chemistry and biology, serving, for example, as antibiotics, as ligands for metal-based catalysts, as catalysts themselves, and as chiral auxiliaries.[1] With respect to the catalytic enantioselective synthesis of sulfur-containing molecules, the conjugate addition of thiols to the β position of α,β-unsaturated carbonyl compounds has been the focus of intense interest.[2] Furthermore, there has been recent progress in catalytic asymmetric sulfenylation α to a carbonyl group.[3] In contrast, we are not aware of any methods for catalytic enantioselective sulfenylation of the γ position of carbonyl compounds.[4]

Trost and others have established that phosphines can catalyze certain γ additions of carbon, nitrogen, and oxygen nucleophiles to 2,3-allenoates and/or 2-alkynoates;[5−8] on the other hand, the corresponding γ additions of sulfur nucleophiles have not been achieved. In this report, we describe a method that not only accomplishes γ functionalizations with this new family of nucleophiles but also provides highly enantioenriched products (eq 1).[9−12]



(1)

In the case of the carbon, nitrogen, and oxygen nucleophiles that have previously been employed in phosphine-catalyzed γ additions, there is generally no reaction between the nucleophile and an allenoate at room temperature in the absence of a catalyst. In contrast, thiols do react with allenoates, but not to afford the γ-addition product (Table 1, entry 1); instead, the uncatalyzed process leads to addition of the thiol at the β position.

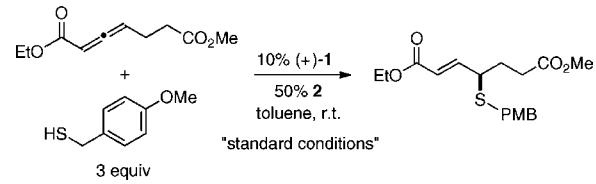
Nevertheless, through the use of an appropriate catalyst, the regioselectivity of the addition process can be altered to generate the desired γ-addition product not only in good yield but also with very good enantioselectivity. In particular, chiral bisphosphine TangPhos (**1**), originally developed by Zhang as a ligand for Rh-catalyzed asymmetric hydrogenations of olefins,[13] along with a carboxylic acid additive,[14] serves as a useful catalyst system, furnishing the γ-sulfenylated product in 89% yield and 92% ee (Table 1, entry 2). To the best of our knowledge, this is the first application of **1** as an effective chiral nucleophilic catalyst.[15,16]

In the absence of carboxylic acid **2**, or when **2** is replaced by phenol,[5d] very little γ-addition product is observed (Table 1, entries 3 and 4). Other chiral phosphines (e.g., see entries 5[5d] and 6[7d]) give lower yields and/or ee. Use of 1.1 equiv of thiol leads to a small loss in yield and no change in enantioselectivity (entry 7).

This phosphine-catalyzed asymmetric γ addition of thiols proceeds in good yield for an array of allenoates (Table 2).[17] Thus, carbon−sulfur bond formation occurs with high ee in the presence of a variety of functional groups, including alkenes, alkynes, ethers, acetals, esters, and halides.

This method for the catalytic asymmetric synthesis of sulfides is versatile with respect to the thiol as well as the allenoate (Table

Table 1. Effect of Reaction Parameters on the Catalytic Asymmetric γ Addition of Thiols to Allenoates[a]



entry	change from the "standard conditions"	yield (%)[b]	ee (%)
1	no (+)-**1**, no **2**	0[c]	–
2	none	89	92
3	no **2**	<5	–
4	PhOH instead of **2**	<5	–
5	(*S*)-**3** instead of (+)-**1**	<5	–
6	(*S*)-**4** instead of (+)-**1**	81	80
7	1.1 instead of 3 equiv of thiol	80	92

[a] All data are averages of two experiments. [b] Determined by ^{1}H NMR analysis with dibromomethane as an internal standard. [c] Addition occurred predominantly at the β position.

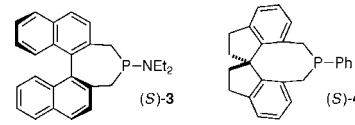
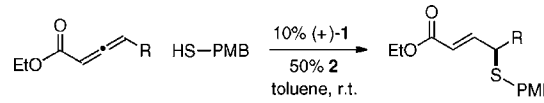


Table 2. Catalytic Asymmetric γ Addition of Thiols to Allenoates: Scope with Respect to the Allenoate[a]



entry	R	yield (%)[b]	ee (%)
1	*n*-Pr	80	91
2	CH_2	78	92
3	$(CH_2)_7$	81	91
4	$(CH_2)_2$	87	85
5	$(CH_2)_4OBn$	81	93
6	$(CH_2)_2$ Ph	89	90
7	$(CH_2)_2CO_2Me$	72	92
8	$(CH_2)_3Cl$	82	93

[a] All data are averages of two experiments. [b] Yield of purified product.

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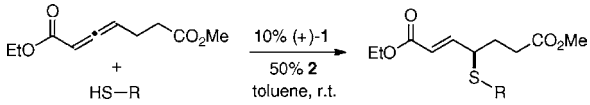
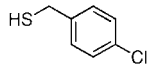
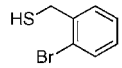
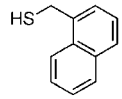
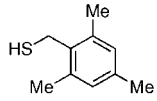
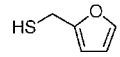
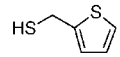
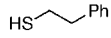
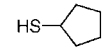
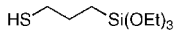
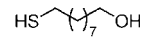
3). A variety of substituted benzyl thiols, including hindered substrates, add to the γ position in good yield and ee (entries 1−5). Furthermore, heterocycles are compatible with the reaction conditions (entries 6 and 7). TangPhos also efficiently catalyzes the asymmetric γ addition of thiols that are not benzylic (entries 8−11); for the substrate illustrated in entry 11, exclusive γ addition by sulfur (none by oxygen[7]) is observed.

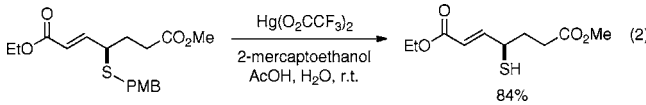
Table 3. Catalytic Asymmetric γ Addition of Thiols to Allenoates: Scope with Respect to the Thiol[a]

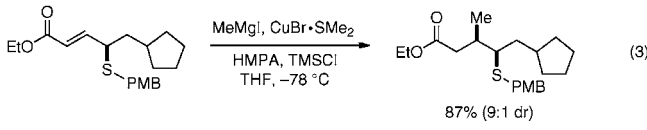


entry	HS−R	yield (%)[b]	ee (%)
1	HS−Bn	77	92
2		77	90
3		76	92
4		77	94
5		83	95
6		72	92
7		67	89
8		78	87
9		80	93
10		73	85
11		79	88

[a] All data are averages of two experiments. [b] Yield of purified product.

The enantioenriched sulfides produced via phosphine-catalyzed γ additions to allenoates can be transformed into other useful compounds. For example, the sulfide can be converted into a thiol (eq 2), or highly stereoselective functionalizations of the olefin can be achieved (eq 3).





In summary, the first method for catalytic asymmetric γ sulfenylation of carbonyl compounds has been developed. Thus, in the presence of an appropriate catalyst, thiols not only add to the γ position of allenoates, overcoming their propensity to add to the β position in the absence of a catalyst, but do so with very good enantioselectivity. Sulfur nucleophiles are now added to the three families of nucleophiles (carbon, nitrogen, and oxygen) that had earlier been shown to participate in catalyzed γ additions. The phosphine catalyst of choice, TangPhos, had previously only been employed as a chiral ligand for transition metals, not as an efficient enantioselective nucleophilic catalyst. The development of additional phosphine-catalyzed asymmetric reactions is underway.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Notes: (a) In all cases, the *Z* isomer of the product was not detected. (b) On a gram scale, the reaction illustrated in entry 3 of Table 2 proceeded in 87% yield (purified product) and 91% ee. (c) At partial conversion, no kinetic resolution of the allenoate was observed. (d) By ^{31}P NMR spectroscopy, we determined that TangPhos is not protonated by acid **2** in toluene at room temperature. ^{31}P NMR spectroscopy at −40 °C indicated that when TangPhos (10%), acid **2** (50%), and an allenoate are mixed, two compounds may be predominant [neither is TangPhos itself; compound 1: δ 79 (d), 57 (d); compound 2: δ 64 (s)]; upon addition of a thiol, both appear to be transformed into the γ-addition product, with liberation of TangPhos. Under the standard reaction conditions, the same resonances were observed by ^{31}P NMR spectroscopy during the reaction (upon cooling to −40 °C; there was no resonance due to TangPhos), and TangPhos reappeared when the reaction was complete. (e) TangPhos is susceptible to oxidation: after exposure to air for 3 days at room temperature, quantitative conversion to the bis(phosphine oxide) was observed by ^{31}P NMR spectroscopy. The bis(phosphine oxide) is not an effective catalyst for γ additions of thiols to allenoates. (f) In an initial investigation, γ additions of ArSH proceeded in low yields under our standard conditions. (g) Preliminary studies with truncated (monophosphine) relatives of TangPhos furnished little of the γ-addition product.

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