

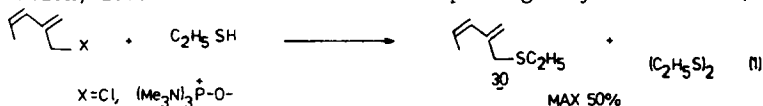
SYNTHESIS OF ALLYL SULFIDES VIA A PALLADIUM MEDIATED ALLYLATION

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SUMMARY: A mild chemo-, regio-, and diastereoselective substitution of allyl carbonates and vinyl epoxides by sulfur nucleophiles catalyzed by palladium can overcome difficulties in and complement conventional displacement without poisoning of the catalyst.

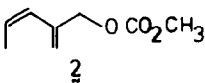
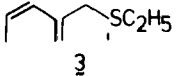
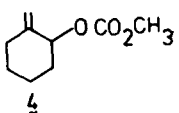
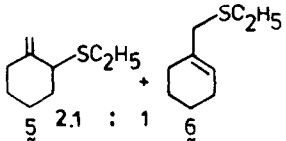
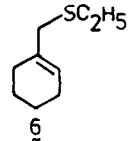
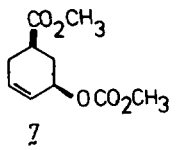
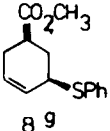
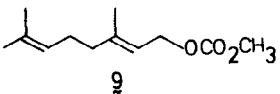
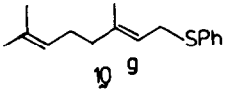
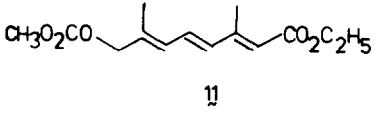
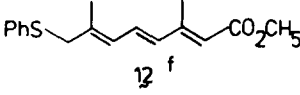
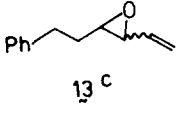
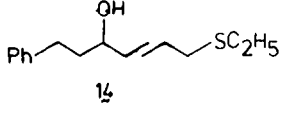
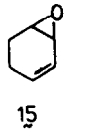
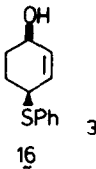
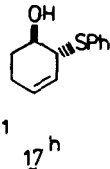
As part of a synthetic study aimed at the pumiliotoxin family of alkaloids **1a**, we found the need for allyl sulfide **3**.^{1b} Standard procedures for this transformation, i.e. treatment of the corresponding allyl chloride (eq. 1) or



allyloxyphosphonium salt with ethyl thiolates resulted in only 50% conversion to allylsulfide **3** with concomitant production of diethyl disulfide. This problem appeared to us to stem from an electron transfer mechanism which may relate to the degree of electron withdrawing ability of the leaving group of the allylating substrate. Therefore, it was reasoned that a poorer leaving group may avoid this problem, but this solution suffers from the unreactivity of such substrates. Transition metal catalysis should resolve this dilemma. Allyl carbonates are readily available substrates that react sluggishly with most nucleophiles, but are good allylating agents in the presence of a Pd(o) catalyst.^{2,3} Thus, we envisioned allyl carbonate **1** and an appropriate sulfur nucleophile providing allyl sulfide **3** in the presence of a Pd(o) catalyst. The problem of catalytic poisoning by sulfur -- although a nuisance in heterogeneous catalysis -- appears less severe in homogeneous catalysis since each metal atom is an "active site", and ligand exchange is more facile. A recent report⁴ utilizing O-allyl S-alkyl xanthates prompts us to report that sulfur nucleophiles can be employed directly with simpler allyl carboxylates and vinyl epoxides, and resolves the problem of the synthesis of the dienyl sulfide **3**. The method applies both to alkyl and aryl sulfides. The importance of allylsulfides as synthetic intermediates makes this simple chemo- and diastereoselective route quite useful.

Initially reacting **2** with ethanethiol in the presence of (dba)₃Pd₂.CHCl₃ (**1**)⁵ and dppp⁶ in THF at room temperature led to a 79% yield of the desired sulfide **3**. Attempts to scale up this reaction led to irreproducible results which also occurred upon attempted repetition of small scale experiments. On the other hand, the ethylthiotrimethylsilane⁷ reacted smoothly under otherwise identical conditions to give sulfide **3** in a totally reproducible fashion.⁸ In

Table. Pd Mediated Allyl Sulfide Synthesis^a

Entry	Substrate	Nucleophile	Products ^d	Yield
1 ^b		$C_2H_5Si(CH_3)_3$		87% (95%) ^e
2		$C_2H_5Si(CH_3)_3$	 5 : 2.1 : 1 	57%
3		$PhSi(CH_3)_3$		70%
4		$PhSi(CH_3)_3$		68%
5		$PhSi(CH_3)_3$		91%
6		$C_2H_5Si(CH_3)_3$		81%
7		$PhSi(CH_3)_3$	 16 : 3.4 : 1 	64%

a) All reactions were performed utilizing $(dba)_3Pd_2 \cdot CHCl_3$ [5 mol% Pd(o)] and 30 mol% of triisopropyl phosphite in THF at rt unless otherwise stated.

b) In this run, dppp was employed as ligand.

c) A 2:1 E/Z mixture was employed.

d) All new compounds have been fully characterized spectrally and elemental composition established by high resolution mass spectrometry.

e) Employing a 12.1 mmol scale with 1 mol % of palladium catalyst and 3 mol % of dpe increases the isolated yield to 95%.

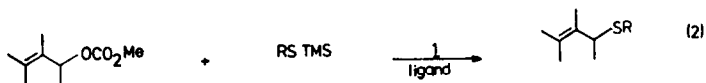
f) The nmr spectrum reveals the presence of a very minor isomer whose limited amount precluded its full characterization.

g) In these reactions, an additional portion of catalyst was added after 12 hrs to attain complete conversion to products.

h) This product arises via a non-palladium catalyzed reaction.

this case, scaling up the reaction which also entailed decreasing the amount of Pd(o) from 5 mol% to 1 mol% increased the yield from 87% to 95%.

The effectiveness of this reaction in a case which proceeds poorly in a classical displacement approach led us to explore its generality as outlined in the Table and eq. 2. It is effective with both alkyl- and arylthio nucleophiles

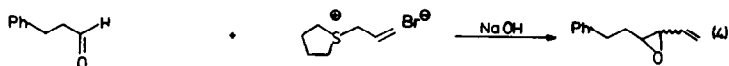


(entries 1 and 2 versus 3-5). The reaction proceeds with net retention of configuration (entry 3) and with excellent geometrical control with trisubstituted olefins (entries 4 and 5). Michael-type processes do not compete with the substitution (entry 5).

Other normal substrates for palladium catalyzed reactions such as sulfones⁹ and nitro¹⁰ compounds are anticipated to proceed in similar fashion. We examined vinyl epoxides¹¹ (eq. 3 and entries 6 and 7). It is interesting to



note that only 1,4 substitution results in the palladium catalyzed reaction. In the case of vinyl epoxide 15, it is sufficiently reactive that a non-palladium catalyzed reaction which leads only to 17 cannot be completely suppressed. However, this example shows the complementarity of the palladium and non-palladium catalyzed reactions. Although vinyl epoxide 13 is a mixture of geometric isomers, only a single isomer 14 results. This example also illustrates the utility of this approach, since the vinyl epoxide 13 is so



easily available as outlined in eq. 4.¹²

The following is a preparative experimental procedure: allyl carbonate 2 (1.88g 12.1 mmol) and ethylthiotrimethylsilane (2.10 g, 15.7 mmol) were dissolved in 21 mL of THF and placed under an atmosphere of N₂. In a separate flask, (dba)₃Pd₂(CHCl₃)⁶ (63 mg, 0.061 mmol, 1 mol% Pd(o)) and dppp (151 mg, 0.366 mmol) were dissolved in 3.0 mL of THF under N₂. When this solution sustained a yellow color (5 min), it was added via syringe to the allyl carbonate solution. The reaction mixture was stirred for 9 hr at rt, then concentrated in vacuo. Chromatography on silica gel with hexane as eluent provided 1.63 g (95%) of allyl sulfide 3 as a colorless oil. With the vinyl epoxide substrates (entries 6 and 7), it was necessary to stir the crude product in a potassium carbonate/methanol mixture for 1 hr to cleave the silyl

ether. Extractive isolation and chromatography as above gave the hydroxy sulfides 14 and 16, 17.

In conclusion, we have described a new method for the synthesis of allyl sulfides. This method is general in substrate and nucleophile and offers a practical alternative to more conventional procedures, along with the chemo, regio, and stereoselectivity of a palladium mediated allylation.

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