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Palladium-Catalyzed Regioselective Addition of Thiophenol to Conjugated Enynes. Efficient Syntheses of 2-(Phenylsulfinyl) and 2-(Phenylsulfonyl) 1,3-Dienes

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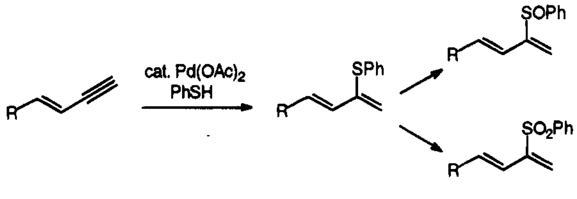
Summary: Palladium-catalyzed addition of thiophenol to conjugated enynes with a terminal triple bond occurs in a regioselective manner to produce 2-(phenylthio) 1,3-dienes, which were selectively oxidized to either 2-(phenylsulfinyl) or 2-(phenylsulfonyl) 1,3-dienes by proper choice of reaction conditions and oxidant.

Electron-deficient conjugated dienes have recently attracted considerable interest as useful building blocks in organic synthesis.[1−6] A number of such dienes have been reported in the literature, and in particular, 2-(arylsulfonyl) 1,3-dienes have proved to be versatile intermediates.

We have previously developed two general methods for the regioselective preparation of 2-(phenylsulfonyl) 1,3-dienes, which involve metal-mediated (Hg or Se) addition to conjugated dienes.[7,8] Because of the use of stoichiometric amounts of metal reagent in these processes, which has drawbacks on a large scale synthesis, an apparent objective was to develop a metal-catalyzed process. In this paper we report a regioselective palladium-catalyzed addition of thiophenol to conjugated enynes, which provides an entry to synthetically useful 2-(phenylsulfinyl) and 2-(phenylsulfonyl) 1,3-dienes. It is worthwhile noting that also the parent 2-(phenylthio) 1,3-dienes have found wide use in organic synthesis, mainly in Diels−Alder reactions.[9]

Transition-metal catalyzed addition of nucleophiles to conjugated dienes often occurs in the 1-position with formation of a (π-allyl)metal complex.[10] Conjugated dienes therefore seemed unsuitable as substrates for metal-catalyzed preparation of 2-(phenylsulfonyl) 1,3-dienes, since this approach requires addition of PhS^- or $PhSO_2^-$ to the 2-position of the diene. We therefore turned our attention to conjugated enynes to avoid the inherent selectivity for attack at the 1-position. In view of the ready palladium-catalyzed addition of aromatic thiols to acetylenes[11] we decided to study the palladium-catalyzed reaction of thiophenol with conjugated enynes.

Scheme 1



Reaction of enyne **1** with thiophenol in THF at 50 °C in the presence of catalytic amounts of $Pd(OAc)_2$ afforded phenylthio diene **6** in 72% isolated yield (Table 1, entry 1). The addition of thiophenol was highly regioselective, and only the triple bond was attacked by the sulfur nucleophile. This reflects the higher reactivity of the carbon−carbon triple bond over the carbon−carbon double bond in palladium(II)-promoted nucleophilic addition.[12] Importantly, only the regioisomer arising from sulfur attack at carbon-2 of the 3-en-1-yne was observed. Other acyclic conjugated enynes such as **2** and **3** were also regioselectively transformed into the corresponding 2-(phenylthio) 1,3-dienes **7** and **8a**, respectively, via the palladium-catalyzed addition of thiophenol (Table 1). The reaction of cyclic substrate **4** and **5** also went smoothly to give **9** and **10**, respectively. Oxidation of the 2-(phenylthio) 1,3-dienes obtained to the corresponding 2-(phenylsulfonyl) 1,3-dienes was done employing either oxone[13] or *m*-chloroperbenzoic acid (m-CPBA). Thus, sulfide **6** was selectively oxidized by oxone to sulfone **11** (Table 1). Oxidation of sulfides **7**, **8b**, **9**, and **10** to their sulfones required the use of m-CPBA for a good selectivity.

Attempts to add thiophenol to enynes with an internal triple bond in the palladium-catalyzed reaction were unsuccessful. In the case of 2-methyl-1-dodecen-3-yne only starting material was recovered using the usual reaction conditions. Other conditions will be pursued.

The phenylthio dienes were also readily oxidized to the corresponding 2-(phenylsulfinyl) 1,3-dienes by the use of

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(13) Oxone, a complex of $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$, was obtained from Aldrich.

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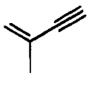
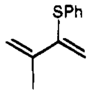
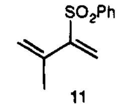
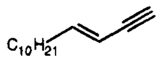
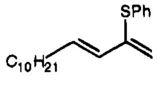
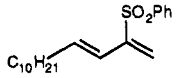
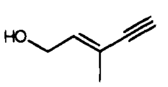
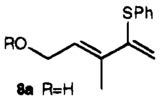
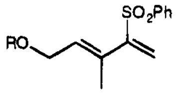
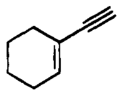
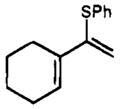
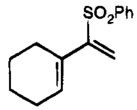
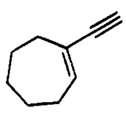
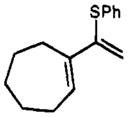
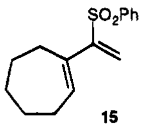
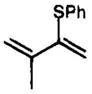
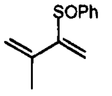
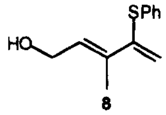
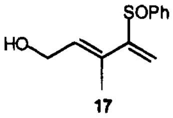
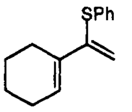
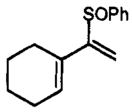
Table 1. Regioselective $Pd(OAc)_2$-Catalyzed Thiophenol Addition to Terminal Conjugated Enynes Followed by Regioselective Oxidation of the Produced 2-(Phenylthio) 1,3-Dienes to the Corresponding 2-(Phenylsulfonyl) 1,3-Dienes

entry	enyne	condns[a]	sulfide diene	yield[b] (%)	condns[c]	sulfone diene	yield[d] (%)
1	 1	A, 50 °C, 14 h	 6	72	C, RT, 3 h	 11	78
2	 2	A, 50 °C, 16 h	 7	41(61[e])	D, 0 °C, 2 h	 12	71
3	 3	A, 60 °C, 16 h	 8a R=H 8b R=COCH$_3$	75	D[f], 0 °C, 4 h	 13 R=COCH$_3$	65
4	 4	B, 50 °C, 18 h	 9	64	D, RT, 2.5 h	 14	73
5	 5	B, 50 °C, 18 h	 10	50[g]	D, 0 °C, 2.5 h	 15	73

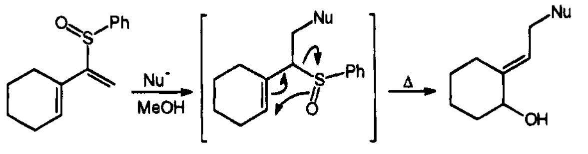
[a] A: Enyne (1.00 mmol), PhSH (1.00 mmol), $Pd(OAc)_2$ (0.02 mmol) in THF (0.5 mL). B: Enyne (1.00 mmol), PhSH (1.10 mmol), $Pd(OAc)_2$ (0.10 mmol) in THF (1.5 mL). [b] Isolated yield based on the enyne. [c] C: Oxone in H_2O / MeOH. D: MCPBA in CH_2Cl_2. [d] Isolated yield based on phenylthiodiene. [e] Yield based on converted enyne. [f] Protection of the activating allylic hydroxy group was necessary to avoid epoxidation. [g] Yield was detemined from the crude reaction mixture (^{1}H NMR).

Table 2. Regioselective Oxidation of the 2-(Phenylthio) 1,3-Dienes to the Corresponding 2-(Phenylsulfinyl) 1,3-Dienes

entry	sulfide diene	condns[a]	sulfoxy diene	yield[b] (%)
1	 6	10 min	 16	67
2	 8	3 h	 17	62
3	 9	50 min	 18	60

[a] Oxone in MeOH / H_2O at 0 °C. [b] Isolated yield based on phenylthiodiene.

a shorter reaction time and less oxidant. Three examples are given in Table 2 where diene sulfides **6**, **8**, and **9** were oxidized to their corresponding sulfoxides employing oxone as the oxidant. Such sulfoxide dienes have recently attracted attention as versatile synthons and building blocks,[6,14,15] and the chirality at sulfur makes them potentially useful in asymmetric synthesis.[6,15] An obvious application is in cycloaddition reactions. Another important synthetic application of these dienes involves Michael addition of a nucleophile and subsequent [2,3] sigmatropic rearrangement of the allyl sulfoxide produced. In this way sulfoxide diene **18** was transformed



18

19a Nu = OMe (85%)
b Nu = CH(CO$_2$Me)$_2$ (77%)[16]

to product **19** employing methoxide and dimethyl malonate anion as nucleophiles. This constitutes a useful tandem 1,4-functionalization of the diene.

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Supplementary Material Available: Experimental procedures and characterization data (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(16) Compound **19b** was contaminated with 12% of **19a**.