follows a pathway fundamentally different from that suggested for oxidation of vitamin K hydroquinone with molecular oxygen.[2]

Experimental Section

Melting points are uncorrected. Compound 3 was synthesized by Diels-Alder reaction of cyclopentadiene with *p*-benzoquinone using a previously published procedure.[7] The material was recrystallized from hexane to afford bright yellow platelets: mp 78-79 °C (lit.[8] mp 77-78 °C). An authentic sample of 4 was prepared using the procedure described by Alder and co-workers.[3a] Pure 4 was obtained by recrystallization from EtOAc-hexane; this procedure afforded 4 as a colorless microcrystalline solid: mp 118-118.5 °C (lit.[3a] mp 118 °C). Hydrogen peroxide-$^{18}O_2$, purchased from Icon Services, Summitt, NJ, was found by mass spectroscopic analysis to contain 80% $^{18}O_2$ isotopic enrichment.

Gas Chromatography and Mass Spectroscopy. A Hewlett-Packard Model 5890, Series II, gas chromatograph (GC) connected directly to a Hewlett-Packard Model 5970 mass spectrometer (MS) was employed in this study. The GC column used was a 12-m × 0.2-mm i. d. fused silica capillary column which contained a film (0.33-μm thickness) of 100% dimethyl polysiloxane (Hewlett-Packard, HP-1). The sample was injected into the GC injection port, whose temperature was maintained at 250 °C, while the column temperature was maintained at 80 °C. Forty seconds after the sample had been injected into the GC, the column oven was heated rapidly to its final temperature of 300 °C (heating rate ca. 45 °C/min). The detector temperature was set at 280 °C. Oxygen-free helium was used as carrier gas (inlet pressure 7 psig; flow-rate 55 mL/min).

Reaction of 3 with Basic $H^{18}O$-^{18}OH. To a solution of 3 (17, mg, 0.10 mmol) in absolute EtOH (2 mL) was added with stirring $H^{18}O$-^{18}OH (75 mg, 2.0 mmol) and aqueous 3 M Na_2CO_3 solution (0.3 mL). The reaction mixture was stirred at 50 °C for 5 min, at which time an aliquot (0.2 mL) was withdrawn and quenched by the addition of water (1.0 mL). The resulting mixture was extracted with Et_2O (0.2 mL). To avoid possible oxygen exchange at the carbonyl groups, which might arise by contact with silica gel, the product was not purified by column chromatography. Instead, the ether layer was examined directly by GC/MS analysis. The GC/MS trace displayed a major peak with retention time 3.25 min, which corresponded to that of authentic 4 and which indicated that the reaction had proceeded to completion. The mass spectrum of the product (4) displayed the following peaks, m/z (relative intensity): 192 (M^+, 100), 193 (11.6) and 194 (1.1). Calcd natural abundance ratio for $C_{11}H_{10}O_3$: M^+:M^+ + 1:M^+ + 2 = 100:12.2:1.2.

The remainder of the sample was poured into water (10 mL) and extracted with Et_2O (3 × 5 mL). The combined ether extracts were dried over $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo affording a brown solid (15 mg). The crude product was purified by chromatography on silica gel (10 g) by eluting with 1:4 EtOAc-hexane mixed solvent. Pure 4 (11.2 mg, 58%) was obtained as a colorless microcrystalline solid: mp 117-118 °C (lit.[3a] mp 118 °C). The ^1H NMR spectrum of this material was identical in all respects with that of authentic 4.

Vitamin K Oxide-$^{18}O_1$. Vitamin K (50 mg, 0.11 mmol) and $H^{18}O$-^{18}OH (75 mg, 2.10 mmol) in absolute EtOH (2.5 mL) were combined with 3 M aqueous Na_2CO_3 solution (0.3 mL). The resulting mixture was heated with stirring at 75 °C for 1 h. The reaction mixture was poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined ether layers were examined by GC-MS. The GC-MS trace contained a peak with retention time 7.9 min whose mass spectrum displayed the following peaks, m/z (relative intensity): 468 (M^+, 100), 469 (33.3), and 470 (6.9). Calcd natural abundance ratio for $C_{31}H_{46}O_3$: M^+:M^+ + 1:M^+ + 2 = 100:34.4:6.3.

The combined ether extracts were dried over $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo, affording a yellow oil (52.3 mg). The crude product was purified by column chromatography on silica gel (10 g), eluting with 1:19 EtOAc-hexane mixed solvent. Pure vitamin K oxide (45.4 mg, 88%) was obtained as a colorless oil with spectral properties identical to those of an authentic sample.[2]

Control Experiments. 1. Synthesis of 1-^{18}O under Anhydrous Conditions. To a mixture of 1 (10 mg) and 90% $H_2{}^{18}O_2$ (20 μL, Icon Services) in absolute EtOH (2.5 mL) was added Na_2CO_3 (20 mg), and the resulting mixture was heated at 60 °C. The progress of the reaction was followed by GC-MS, which indicated that the reaction had proceeded to 50% completion after 1 h. The mass spectrum of the reaction mixture confirmed the presence of vitamin K oxide-^{18}O with its molecular ion at m/z 468, M^+ + 1 peak at m/z 469 with relative intensity 34.3, and M^+ + 2 peak at m/z 470 with relative intensity 6.1. Calcd ratio of intensities M^+:M + 1:M^+ + 2 = 100:34.3:6.3).

2. Nonexchange of Vitamin K Oxide-^{18}O with H_2O. To a solution of vitamin K oxide-^{18}O (8.8 mg) in absolute EtOH (0.5 mL) was added to a solution of Na_2CO_3 (20 mg) in water (60 μL). The reaction mixture was stirred at 60 °C for 3 h, at which time the progress of the reaction was checked by GC-MS. The mass spectrum revealed no change in the relative intensities of the mass spectral peaks of the reaction product when compared with those of starting material. This result indicates that none of the ^{18}O label contained in the starting vitamin K oxide-^{18}O, prepared by oxidation of with $H^{18}O$-^{18}OH, resides in the carbonyl groups.

3. Nonexchange of 4-$^{18}O_1$ with H_2O. To a solution of 1.1 mg (0.0057 mmol) of 4-^{18}O (labeled at the epoxide oxygen by epoxidation of 3 with $H^{18}O$-^{18}OH) in absolute EtOH (0.1 mL) was added a solution of Na_2CO_3 (5 mg) in 20 μL of H_2O. The reaction mixture was stirred at 50 °C for 3 h and then checked by GC/MS. The mass spectrum of the product showed no change in the relative intensities of the peaks at m/z 190 and 192 as compared with the corresponding peaks in the mass spectrum of the starting material 4-$^{18}O_1$.

4. Epoxidation of 3 in $H_2{}^{18}O$. To a solution of 3 (4.0 mg, 0.023 mmol) in absolute EtOH (0.5 mL) was added unlabeled 90% H_2O_2 (15 μL, excess) and a solution of Na_2CO_3 (25 mg) in 0.1 mL of $H_2{}^{18}O$ [96% ^{18}O-enriched (Icon Services)]. The reaction mixture was stirred at 50 °C for 5 min and then checked by GC/MS. The mass spectrum of the product 4 displayed the following peaks, m/z (relative intensity): 190 (M^+, 100), 191 (13.3), and 192 (11.2). Calcd natural abundance ratio for $C_{11}H_{10}O_3$: M^+:M + 1:M^+ + 2 = 100:12.2:1.2.

5. Exchange of Carbonyl-Labeled 4-$^{18}O_1$ with H_2O. To a solution of 1.5 mg (0.0038 mmol) of 4 previously exchanged with $H_2{}^{18}O$ (vide supra) in 0.2 mL of absolute EtOH was added a solution of Na_2CO_3 (5 mg, excess) in 20 μL of H_2O. The reaction mixture was stirred at 50 °C for 30 min and then checked by GC/MS. The mass spectrum of the product indicated that the intensity of the peak at m/z 192 had become reduced to 5.5% of the parent ion at m/z 190. The sample was then stirred with the same concentration of fresh aqueous sodium carbonate solution (20 μL) at 50 °C for 3 h. The mass spectrum of the product displayed a peak at m/z 192 of normal intensity (1.2%).

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Tandem Pummerer-Type Rearrangement and Nickel-Catalyzed Alkylative Olefination of the Cyclic Dithioacetal *S*-Oxides of Aromatic Aldehydes with Grignard Reagents

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The nickel-catalyzed cross-coupling of various organosulfur compounds with Grignard reagents has been extensively studied.[1] However, to our surprise, we found

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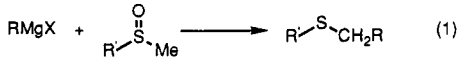
Table I. Nickel-Catalyzed Cross Coupling of 1 with Grignard Reagents

Ar	n	Grignard reagent	3 or 5 (% yield)	4 (% yield)
1-naphthyl (1a)	1	MeMgI	3a (68)[a]	4a (2)[b]
2-naphthyl (1b)	1	MeMgI	3b (63)[c]	4b (3)[d]
4-MeC_6H_4 (1c)	1	MeMgI	3c (54)[e]	4c (3)[f]
3,4-$(MeO)_2C_6H_3$ (1d)	1	MeMgI	3d (48)[g]	4d (4)[h]
2,5-$(MeO)_2C_6H_3$ (1e)	1	MeMgI	3e (51)[i]	
4-MeC_6H_4 (1f)	2	MeMgI	3c (50)	4c (2)
2,5-$(MeO)_2C_6H_3$ (1g)	2	MeMgI	3e (48)	
1-naphthyl (1a)	1	Me_3SiCH_2MgCl	5a (66)[j]	
2-naphthyl (1b)	1	Me_3SiCH_2MgCl	5b (67)[k]	

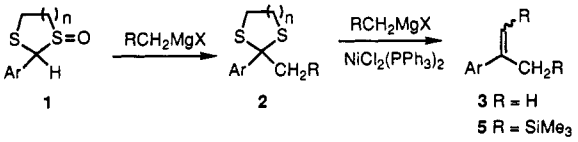
[a] Reference 9. [b] Reference 10. [c] Reference 11. [d] Reference 12. [e] Reference 13. [f] Reference 14. [g] Reference 15. [h] Reference 16. [i] Reference 17. [j] E/Z = 1:2, ref 15. [k] E/Z = 2:3, ref 15.

only a few reports which concern the reaction of sulfoxides with Grignard reagents. For example, diaryl sulfoxides react with aryl Grignard reagents in the presence of $NiCl_2(PPh_3)_2$ catalyst to afford the corresponding cross-coupling products.[2a] On the other hand, under similar conditions, secondary Grignard reagents reduce the carbon–sulfur bonds of sulfoxides.[2b,c] Furthermore, the ligand coupling reactions[3] of sulfoxides, which give products of carbon–carbon bond formation, have been shown to be highly useful in organic synthesis. Sulfoxides can also undergo various fascinating base-catalyzed rearrangements. For example, it has been reported that upon treatment with Grignard reagents, sulfoxides which bear an α-hydrogen atom undergo a Pummerer-type rearrangement, the product of which, in turn, reacts with excess Grignard reagent to form a thioether (eq 1).[4] We believed that



(1)

dithioacetal S-oxides 1 would behave similarly. That is, we believed that, in the presence of a nickel catalyst, 1 would react with a Grignard reagent to afford 2 which then would undergo a nickel-catalyzed cross coupling with the Grignard reagent[1b,5] to form an isopropenylated arene (eq 2). Therefore, we report the details of a new synthetic application of the dithioacetal S-oxides of aromatic aldehydes.



(2)

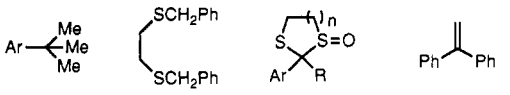
Results and Discussion

Refluxing a benzene/diethyl ether solution of 1 and MeMgI (5 equiv) for 16 h in the presence of $NiCl_2(PPh_3)_2$ (6 mol %) gave 3. Excess Grignard reagent was necessary to drive the reaction to completion. The results are summarized in Table I. Occasionally, *tert*-butylarenes 4 were isolated as side products. It appears that the size of the dithioacetal S-oxide ring has no effect on reactivity. Thus, sulfoxides derived from either dithiolanes or dithianes give similar yields of the expected products. When the Grignard reagent was Me_3SiCH_2MgCl, the bissilanes 5 were obtained in satisfactory yields.

Table II. Nickel-Catalyzed Cross Coupling of 7 with MeMgI

Ar	R	n	product	yield, %
1-naphthyl (7a)	Me	1	(3a)	61
2-naphthyl (7b)	Me	1	(3b)	62
4-MeC_6H_4 (7c)	Me	1	(3c)	62
2-fluorenyl (7d)	Me	1	(3f)[a]	76
2-fluorenyl (7e)	Me	2	(3f)	65
Ph (7f)	Ph	1	(8)[b]	57
Ph (7g)	Ph	2	(8)	67

[a] Reference 18. [b] Reference 19.



4 6 7 8

The fate of the sulfur-containing moiety of 1 was also established. Thus, 1a was allowed to react with MeMgI in the presence of nickel catalyst as described above, followed by quenching the reaction with aqueous sodium hydroxide and treating the mixture of products with excess benzyl bromide to afford bisthioether 6 in 44% yield. This result indicates that 2 is a likely intermediate in the conversion of 1 into 3.

A nickel–hydridic species generated in situ is known to be effective for the reductive cleavage of the carbon–sulfur bonds of sulfoxides.[6] Several pieces of evidence suggest that thioethers are the intermediates in these reactions. Unlike 1, compounds 7 cannot undergo a Pummerer-type rearrangement which would introduce an alkyl group at the C-2 position. It was interesting to compare the behavior of 7 with that of 1. Thus, treatment of 7 with MeMgI in the presence of a catalytic amount of $NiCl_2(PPh_3)_2$ in refluxing benzene/diethyl ether for 16 h gave the corresponding compounds 3 (Table II). The extruded sulfurated fragment was trapped in a manner similar to that described above. For example, 6 was isolated in 40% yield from the reaction of 7c with MeMgI.

There appear to be at least two ways whereby compounds 7 can be converted into 3. It may be that compounds 7 are first reduced to compounds 2. It is well-known that sulfoxides can be reduced to sulfides under mild conditions. The "normal" nickel-catalyzed olefination of compounds 2[1,5] would then give compounds 3. Alternatively, the direct oxidative addition of 7 with the Ni(0) species generated in situ, followed by a process similar to that in the "normal" olefination, could give compounds 3 directly. The sulfurated fragment that is liberated would be transformed, in situ, into a thiolate ion, which upon reaction with benzyl bromide would give the thioether 6.

In summary, our results indicate that the nickel-catalyzed reaction of the cyclic dithioacetal oxide of aromatic aldehyde (ketone) with a Grignard reagent can proceed via two different pathways. Thus, whenever a Pummerer-type rearrangement is favored by the presence of an acidic proton at C-2, as in compounds 1, tandem rearrangement and alkylative olefination occurs to give compounds 3. Compounds 1 can thus be considered to be synthetic equivalents of orthothioesters, which are known to undergo

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nickel-catalyzed alkylative olefination.[15] On the other hand, when a Pummerer-type rearrangement is not favored, as in the case with compounds 7, a nickel-catalyzed olefination occurs directly.

Experimental Section

General Procedure for the Nickel-Catalyzed Cross-Coupling of the Cyclic Dithioacetal *S*-Oxides 1 and 7 with MeMgI. To a solution of dithioacetal *S*-oxide[8] (1.0 mmol), $NiCl_2(PPh_3)_2$ (0.06 mmol), and benzene (10 mL) under N_2 was added, in one portion, MeMgI (2.5 mL of a 2 M solution in Et_2O, 5 mmol). The mixture was refluxed for 16 h. The cooled mixture was then poured into saturated aqueous NH_4Cl. The whole was extracted with Et_2O (3 × 20 mL). The combined extracts were washed (2 × 20 mL of 10% aqueous NaOH, water, and brine) and dried ($MgSO_4$). The solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane) to afford 3. Occasionally, *tert*-butylarenes 4 were isolated as side products. The separation of compounds 3 and 4 was achieved by preparative GC (6 ft 30% SE 30).

Isolation of the Bisbenzyl Thioethers of 1,2-Ethanedithiol (6) from the Reaction of 1a with MeMgI. To a solution of 1a (248 mg, 1.00 mmol), $NiCl_2(PPh_3)_2$ (39 mg, 0.06 mmol), and benzene (10 mL) under N_2 was added, in one portion, MeMgI (2.5 mL of a 2 M solution in Et_2O, 5.0 mmol). The mixture was refluxed for 16 h. Then the reaction was quenched by adding 10% aqueous NaOH (3.0 mL) and BnBr (400 mg, 2.3 mmol). The mixture was then refluxed for 4 h, whereupon it was cooled to rt and was poured into water (10 mL). The whole was extracted with Et_2O (3 × 20 mL). The combined extracts were washed (water, brine) and dried ($MgSO_4$). The solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (hexane/EtOAc (9:1)) to give 5[20] (121 mg, 44%).

Isolation of 6 from the Reaction of 7c with MeMgI. In a manner similar to that described above, a solution of 7c (248 mg, 1.00 mmol), $NiCl_2(PPh_3)_2$ (36 mg, 0.06 mmol), and benzene (10 mL) was treated with MeMgI (2.5 mL of a 2 M solution in Et_2O, 5.0 mmol). The mixture was refluxed for 16 h. The reaction was then quenched by adding 10% aqueous NaOH (3.0 mL) and BnBr (400 mg, 2.3 mmol) to give 5 (110 mg, 40%).

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Registry No. 1a, 141118-36-7; 1b, 141118-37-8; 1c, 139268-27-2; 1d, 139268-31-8; 1e, 139268-32-9; 1f, 141118-38-9; 1g, 141118-39-0; 3a, 1855-47-6; 3b, 3710-23-4; 3c, 1195-32-0; 3d, 30405-75-5; 3e, 72667-91-5; 3f, 53744-54-0; 4a, 17085-91-5; 4b, 2876-35-9; 4c, 98-51-1; 4d, 41280-64-2; (*E*)-5a, 128155-64-6; (*Z*)-5a, 128155-68-0; (*E*)-5b, 128155-65-7; (*Z*)-5b, 128155-69-1; 6, 24794-19-2; 7a, 141118-40-3; 7b, 141118-41-4; 7c, 141118-42-5; 7d, 141118-43-6; 7e, 141118-44-7; 7f, 92548-83-9; 7g, 94676-00-3; 8, 530-48-3; $NiCl_2(PPh_3)_2$, 14264-16-5; MeMgI, 917-64-6; Me_3SiCH_2MgCl, 13170-43-9.

Supplementary Material Available: ^1H and ^{13}C NMR data for 3a–f, 4a–d, 5a, and 5b (2 pages). Ordering information is given on any current masthead page.

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