The Addition of Organolithium Reagents to Quinone Silyl Methyl Monoketals. A Useful Expedient in the Synthesis of *p*-Quinols Having Acid-Sensitive Groups

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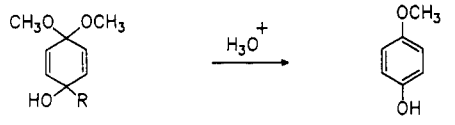
Acid hydrolyses of dimethyl ketals of 4-alkyl- and 4-aryl-4-hydroxy-2,5-cyclohexadienones having an acid-sensitive functionality often afford low or no yields of the respective 4-substituted 4-hydroxy-2,5-cyclohexadienones (*p*-quinols). However, addition of methyl-, *tert*-butyl-, 2-*tert*-butylethynyl-, and aryllithium reagents to 4-(*tert*-butyldimethylsiloxy)-4-methoxy-2,5-cyclohexadienone afforded stereoisomeric mixtures of the corresponding silyl alkyl ketals of *p*-quinols. These silyl alkyl ketals were deblocked by using tetrabutylammonium fluoride to give the corresponding *p*-quinols allowing the preparation of *p*-quinols not attainable from conventional acid-catalyzed ketal hydrolysis.

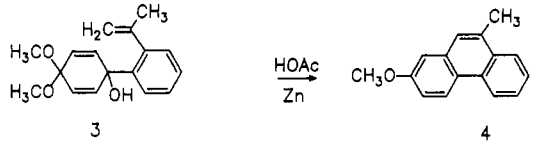
Introduction

Organometallic additions to quinone monoketals[1,2] followed by acid hydrolysis provide an excellent route to *p*-quinols; however, reduction of the quinone monoketal by the organometallic reagent or rearrangement during the ketal hydrolysis serve as limitations on the method. For certain systems, the acidic conditions required for ketal hydrolysis result in fragmentation or rearrangement reactions to the virtual exclusion of *p*-quinol formation. Thus, attempted ketal hydrolysis of **1a,b** gave *p*-methoxyphenol as the major product, presumably via fragmentation of the carbonium ion formed by loss of methanol from the protonated ketal.[3,4] Furthermore, attempted reductive hydrolysis of **3** with zinc in aqueous acetic acid did not give the expected phenol but rather the phenanthrene **4**. This product is formed by cyclization of the olefinic side chain to a carbonium ion intermediate analogous to that involved in the **1** → **2** conversion followed by aromatization. The **3** → **4** cyclization reaction could be a useful route to certain polycyclic aromatic hydrocarbons; however, this process precludes reactions of **3** which proceed via the corresponding *p*-quinol.



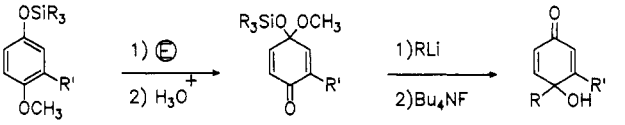
1a. R = 1-ethoxycyclopropyl
b. R = t-Bu

2



3 4

We recently reported that quinone monoketals containing the silyl alkyl ketal linkage were readily available via the anodic oxidation/hydrolysis sequence[5] **5** → **6**. In addition, the preferential hydrolysis of the dimethyl ketal



5 6 7

moiety in bisketals derived from **5** furnishes quinone monoketals of the opposite regiochemistry than that obtained from acid-catalyzed hydrolysis of the quinone bis(dimethyl ketal).[5] Successful addition of organolithium reagents to these compounds followed by deblocking of the silyl alkyl ketal unit under nonacidic conditions could circumvent the side reactions outlined above. This would allow preparation of *p*-quinols not available via conventional acid hydrolysis of *p*-quinol ketals.

Discussion

The reaction of alkyllithium reagents with **6** (R′ = H) afforded a mixture of stereoisomeric quinol ketals in good yield; no desilylation was noted in these reactions. The cis and trans isomers formed in these additions were separated by silica gel chromatography for the reactions of methyl- and phenyllithium with **6** (R′ = H) to verify the structures of the addition products; however, the relative stereochemistry was not assigned. For synthetic purposes, it is convenient to desilylate the crude organolithium addition products and isolate the corresponding quinols by silica gel chromatography. As illustrated in Table I, the overall yields of quinols from **6** (R′ = H) are usually good (55–83%). Especially noteworthy are entries 5–7. The preparation of the *p*-quinols having the 1-ethoxycyclopropyl and *tert*-butyl moieties (entries 5 and 6) could not be accomplished via acid hydrolysis of a ketal linkage because a fragmentation reaction occurred (vida supra, **1** → **2**). In addition, a *p*-quinol[3] having a 2-vinyl-4,5-dimethoxyphenyl substituent was available from **6** (entry 7); contrast this with the **3** → **4** reaction.

The successful addition of *tert*-butyllithium to **6** was somewhat surprising since quinone monoketals are prone to reduction by many organometallic reagents.[1] In fact, reaction of *tert*-butyllithium with the ethylene ketal of 2,6-dimethylbenzoquinone was reported to give solely the reduction product.[6] However, inspection of the ^{1}H NMR spectra of the crude product from the addition of *tert*-butyllithium to the dimethyl and ethylene ketals of benzoquinone at −78 °C showed that reduction was not a

(1) For a survey of organometallic additions to quinone monoketals, see: Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74. Swenton, J. S. In *The Chemistry of Quinoid Compounds*; Rappoport, Z., Patai, S., Eds.; Wiley: New York, 1988; Vol. 2.

(2) For additional examples, see: Capparelli, M. P.; DeSchepper, R. E.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 4953.

(3) We thank Mr. Gary Morrow for allowing inclusion of these results in this manuscript.

(4) Capparelli, M. P.; DeSchepper, R. E.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1987**, 610.

(5) Stern, A.; Swenton, J. S. *J. Org. Chem.* **1987**, *52*, 2763.

(6) Liotta, D.; Saindane, M.; Waykole, L. *J. Am. Chem. Soc.* **1983**, *105*, 2923.

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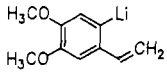
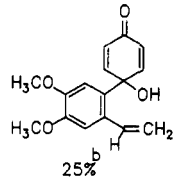
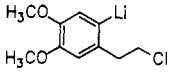
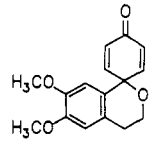
Table I. *p*-Quinols from 4-(*tert*-Butyldimethylsiloxy)-4-methoxy-2,5-cyclohexadienone[a]

entry	RLi	Isomer Ratio	Yield
1	CH_3Li	1:1	83%
2	PhLi	6:1	76%
3	*n*-BuLi	2:1	78%
4	*t*-BuC≡CLi	4:1	57%
5		3:1	70%
6	*t*-BuLi		55%
7			 25%[b]
8			 65%

[a] Isomer ratios were estimated by ^1H NMR. [b] The styrene precursor to the organolithium compounds employed in entry 8 polymerizes rapidly, and the use of this somewhat impure starting compound may be responsible for the lower overall yield recorded in this reaction sequence.

major reaction in these cases either. Thus, the successful addition of *tert*-butyllithium to **6** is not an unusual effect associated with the silyl alkyl ketal linkage.

Summary

The chemistry reported herein establishes that quinone silyl alkyl monoketals complement the quinone dimethyl monoketals for the preparation of *p*-quinol derivatives.

Experimental Section

Melting points were determined in capillaries in a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 283B spectrometer on KBr disks unless otherwise noted. Routine ^1H NMR spectra were determined at 80 MHz on an IBM NR 80 spectrometer using deuteriochloroform as solvent and residual chloroform or tetramethylsilane as standard. Mass spectral and exact mass measurements were obtained by Mr. Richard Weisenberger on a Kratos MS-30 spectrometer. Alumina and silica gel were obtained from E. Merck Co. Base-washed silica gel was prepared by stirring commercial silica gel with 5% concentrated ammonium hydroxide in methanol, filtering, and then drying the silica gel at room temperature (1 Torr) for 24 h. Tetrahydrofuran was purified by distillation from benzophenone ketyl. The term "standard workup" refers to drying the solvent over Na_2SO_4, concentration in vacuo, and drying at ca. 0.5 mmHg until the weight was constant. All other compounds used in this work were either commercially available or else reference is given to their preparation in the Experimental Section. Throughout the Experimental Section, the following abbreviations are used: petroleum ether, bp 35–60 °C (PE), diethyl ether (Et_2O), tetrahydrofuran (THF), and ethyl acetate (EtOAc).

Quinone *tert*-Butyldimethylsilyl Methyl Monoketal (6, R′ = H). This is an improved procedure over that previously reported.[5] To a solution of 1% KOH in CH_3OH (110 mL) maintained at −13 °C in a single-celled electrolysis vessel equipped with nested, cylindrical Pt gauze electrodes[5] was added *p*-methoxyphenyl *tert*-butyldimethylsilyl ether (18.5 g, 77.7 mmol) over 10 h via a syringe pump. During this time and for 2 h after addition a current of 1.4 A was passed through the cell, completely consuming the aryl ether (25% current efficiency). The brown electrolysis solution was poured into a 400-mL beaker, and dry ice was added to neutralize the base. Most of the CH_3OH was removed in vacuo at room temperature, and the reaction mixture was partitioned between PE (150 mL) and water (150 mL). The organic portion was washed further with water (3 × 100 mL) and brine (50 mL). Drying and concentration gave the crude bisketal (ca. 13.6 g) as a yellow oil. To a cold solution of the crude bisketal and $(CH_3)_2CO$ (150 mL) was added chilled 8% HOAc (40 mL) with vigorous stirring. The reaction mixture was allowed to stand for 3 days at −10 °C and 1 day at 5 °C until no bisketal was present by NMR. (Note: To save time, this reaction may be done at room temperature without lowering the yield.) The $(CH_3)_2CO$ solution was poured into 5% $NaHCO_3$ (400 mL) and extracted with PE (3 × 100 mL). The combined PE portions were washed with 5% $NaHCO_3$ (2 × 100 mL) and brine (100 mL), dried over Na_2SO_4, concentrated under reduced pressure, and finally dried at 1 Torr to afford the title compound (10.54 g, 53%) as a pale yellow oil suitable for most purposes. Five grams of this material was filtered through silica gel (50 g) by using 10% Et_2O/PE as eluant to afford colorless material (4.8 g), which was employed in this chemistry.

Methyllithium Addition to 6. To a solution of monoketal (0.751 g, 2.96 mmol) and THF (25 mL) at −78 °C under an atmosphere of dry nitrogen was slowly added methyllithium (2.50 mL, 3.00 mmol) via syringe. The solution was allowed to warm to room temperature over a period of several hours and was stirred for 16 h. After saturated NH_4Cl (5 mL) was added, the reaction mixture was partitioned between Et_2O (20 mL) and brine (30 mL), and the ether portion was dried over Na_2SO_4 and concentrated in vacuo, affording a heavy tan oil (0.830 g). The ^1H NMR spectrum of the oil was consistent with that of a mixture of two isomers in roughly equal amounts. A pure sample of each isomer was obtained as a clear oil by chromatography of a small sample of the crude product on base-washed silica gel [7 × 2 cm column, 10% Et_2O/PE (100 mL), 20% Et_2O/PE (100 mL) as eluant]. The more rapidly eluting isomer showed the following: IR (neat) 1130 (s), 1070 (s), cm^{-1}; ^1H NMR δ 5.98 (d, J_{AB} = 10.3 Hz, 2 H), 5.75 (d, J_{AB} = 10.3 Hz, 2 H), 3.18 (s, 3 H), 1.61 (br, 1 H), 1.34 (s, 3 H), 0.89 (s, 9 H), 0.11 (s, 6 H); mass spectrum, exact mass calcd for $C_{14}H_{26}O_3Si$ *m/e* 270.1651, obsd *m/e* 270.1654.

The more polar isomer showed the following: IR (neat) 2950 (s), 2920 (s), 1130 (s), 1070 (s), 1035 (s), 835 (s), 795 (s), 775 (s) cm^{-1}; ^1H NMR δ 5.95 (d, J_{AB} = 10.3 Hz, 2 H), 5.81 (d, J_{AB} = 10.3 Hz, 2 H), 3.26 (s, 3 H), 1.66 (br, 1 H), 1.34 (s, 3 H), 0.88 (s, 9 H), 0.08 (s, 6 H); mass spectrum, exact mass calcd for $C_{14}H_{26}O_3Si$ *m/e* 270.1651, obsd *m/e* 270.166.

Tetrabutylammonium fluoride (0.35 g, 1.33 mmol) was added to a solution of the crude ketal mixture (0.300 g, 1.11 mmol) in THF (5 mL) at 0 °C under an atmosphere of dry nitrogen. After being stirred for 1 h, the dark solution was poured into Et_2O (50 mL) and washed with brine (3 × 30 mL). Workup gave a tan oil, which was chromatographed on silica gel [6 × 2 cm column, 25% Et_2O/PE (50 mL) and 75% Et_2O/PE (75 mL) as eluant] to afford the quinol (110 mg) as a pale yellow oil[7] (83% based on starting **6**): IR (neat) 1668 (s), 1640 (s), 1620 (s), 855 (s) cm^{-1}; ^1H NMR δ 6.89 (d, J_{AB} = 10.1 Hz, 2 H), 6.12 (d, J_{AB} = 10.1 Hz, 2 H), 2.3 (br, 1 H), 1.48 (s, 3 H); mass spectrum, exact mass calcd for $C_7H_8O_2$ *m/e* 124.0524, obsd *m/e* 124.0526.

Phenyllithium Addition to 6. Phenyllithium (0.9 mL, 1.71 mmol) was added via syringe to a THF (20 mL) solution of monoketal (0.435 g, 1.71 mmol) at −78 °C under an atmosphere of dry nitrogen. The cooling bath was removed, the reaction mixture was stirred for 4 h, and the reaction was quenched with saturated NH_4Cl (5 mL). The reaction mixture was partitioned between Et_2O (20 mL) and brine (30 mL). Workup afforded a light yellow solid (0.608 g), mp 94–100 °C. Recrystallization from PE/Et_2O afforded the major isomer (0.374 g) as a fluffy, white solid: mp 116–116.5 °C; IR (KBr) 1110 (s), 1030 (s), 990 (s), 940 (s) cm^{-1}; ^1H NMR δ 7.55–7.26 (structured m, 5 H), 5.96 (s, 4 H), 3.31 (s, 3 H), 2.11 (s, 1 H), 0.91 (s, 9 H), 0.15 (s, 6 H); mass spectrum, exact mass calcd for $C_{19}H_{28}O_3Si$ *m/e* 332.1807, obsd *m/e* 332.1849.

(7) Wasserman, H. H.; Pickett, J. E. *Tetrahedron* **1985**, *41*, 2155.

Concentration and chromatography of the mother liquor on base-washed silica gel (6.5 × 2 cm column, 10% Et_2O/PE as eluant) afforded the less polar, major isomer (50 mg, total yield 75%) and the more polar, minor isomer (70 mg, 12%): IR (neat) 1120 (br, s) cm^{-1}; ^1H NMR δ 7.55–7.25 (structured m, 5 H), 5.99 (d, J_{AB} = 10.3 Hz, 2 H), 5.90 (d, J_{AB} = 10.3 Hz, 2 H), 3.28 (s, 3 H), 2.86 (br, 1 H), 0.91 (s, 9 H), 0.14 (s, 6 H); mass spectrum, exact mass calcd for $C_{19}H_{28}O_3Si$ m/e 332.1807, obsd m/e 332.1814.

In a separate experiment, addition of phenyllithium (2.2 mL, 4.4 mmol) to a solution of **6** (1.03 g, 4.1 mmol) in THF (25 mL) at −78 °C followed by warming to room temperature over 2 h and conventional workup gave the crude product (1.5 g). To a solution of this material in THF (30 mL) at 0 °C was added TBAF (1.6 g, 6.1 mmol), and the solution was stirred and warmed to room temperature over 20 min. Extractive workup gave a dark liquid, which was chromatographed on silica gel [15 × 2 cm column, eluant 10% Et_2O/PE (150 mL) followed by 50% Et_2O/PE] to afford a light yellow solid (0.57 g, 76%), mp 96–100 °C. Recrystallization from Et_2O/PE gave the analytical sample: mp 103–103.5 °C (lit.[2] mp 98–100 °C); IR (KBr) 1662 (s) cm^{-1}; ^1H NMR δ 7.60–7.25 (m, 5 H), 6.86 (d, J_{AB} = 12 Hz, 2 H), 6.24 (d, J_{AB} = 12 Hz, 2 H), 2.90 (br, 1 H); mass spectrum, exact mass calcd for $C_{12}H_{10}O_2$ m/e 186.0681, obsd m/e 186.0699.

n-Butyllithium Addition to 6. This was performed essentially as described for the addition of methyllithium: the crude product was desilylated and the quinol was purified by silica gel chromatography (gradient elution from 10% Et_2O/PE to 75% Et_2O/PE). This gave the pure quinol (78% from **6**) as a clear oil, which crystallized from PE: mp 49–50.5 °C; IR (KBr) 3400 (br), 1670 (s) cm^{-1}; ^1H NMR δ 6.83 (d, J_{AB} = 10.2 Hz, 2 H), 6.14 (d, J_{AB} = 10.2 Hz, 2 H), 3.15 (br, 1 H), 1.85–0.80 (m, 9 H); mass spectrum, exact mass calcd for $C_{10}H_{14}O_2$ m/e 166.0993, obsd m/e 166.1006.

(2-*tert*-Butylethynyl)lithium Addition to 6. This was performed essentially as described for the addition of methyllithium: the crude product was desilylated and the quinol was purified by silica gel chromatography (gradient elution from 10% Et_2O/PE to 50% Et_2O/PE). This gave the pure quinol (219 mg, 57%). Crystallization from PE afforded white crystalline quinol: mp 105–106 °C; IR (KBr) 1665 (s), 1620 (s) cm^{-1}; ^1H NMR δ 6.85 (d, J_{AB} = 10.1 Hz, 2 H), 6.15 (d, J_{AB} = 10.1 Hz, 2 H), 2.56 (br, 1 H), 1.21 (s, 9 H); mass spectrum, exact mass calcd for $C_{12}H_{14}O_2$ m/e 190.0994, obsd m/e 190.0971.

(1-Ethoxycyclopropyl)lithium[8] Addition to 6. This was performed essentially as described for the addition of methyllithium: the crude product was desilylated and the quinol was purified by silica gel chromatography (gradient elution from 15% Et_2O/PE to 50% Et_2O/PE). This gave the pure quinol (70%) as an oil. The oil crystallized from Et_2O/PE, mp 51–54 °C. The analytically pure material showed the following: mp 57–57.5 °C; IR (neat) 1670 (s) cm^{-1}; ^1H NMR δ 6.91 (d, J_{AB} = 10.25 Hz, 2 H), 6.23 (d, J_{AB} = 10.25 Hz, 2 H), 3.54 (q, J = 7 Hz, 2 H), 2.6 (br, 1 H), 1.07 (t, J = 7 Hz, 3 H), 0.88 (s, 4 H); mass spectrum, exact mass calcd for $C_{11}H_{14}O_3$ m/e 194.0943, obsd m/e 194.0933.

***tert*-Butyllithium Addition to 6.** *t*-BuLi (2.1 mL, 1.7 M in pentane, 3.57 mmol) was added slowly to a THF (24 mL) solution of monoketal (0.840 g, 3.307 mmol) at −78 °C. The mixture was stirred for 15 min and warmed to ca. −10 °C, and the reaction was quenched with water (1 mL). Standard workup gave a pale yellow oil (1.04 g). Reaction of this material dissolved in THF (15 mL) with a solution of TBAF (1.25 g, 4.77 mmol) at −10 °C gave after workup a dark oil, which was chromatographed on base-washed silica gel [2 × 6 cm column, eluted with 10% Et_2O/PE (100 mL) and 30% Et_2O/PE (150 mL)]. The early product containing fractions were contaminated (TLC analysis); however, the later fractions contained quinol (0.300 g, 55%) as a pale yellow solid, pure by TLC, but melting over the range 70–83 °C. Recrystallization of a sample three times from Et_2O/PE afforded pure quinol as white needles. This material was stable at −10 °C but decomposed under vacuum at room temperature, thus preventing a combustion analysis from being obtained. This material showed the following: mp 94–95 °C; IR (KBr) 3340 (s), 1668 (s), 1623 (s) cm^{-1}; ^1H NMR δ 6.98 (d, J_{AB} = 10.4 Hz, 2 H), 6.23 (d, J_{AB} = 10.4 Hz, 2 H), 1.89 (s, 1 H), 1.04 (s, 9 H); mass spectrum, exact mass calcd for $C_{11}H_{14}O_2$ m/e 166.0994, obsd m/e 166.0980.

[2-(2-Chloroethyl)-4,5-dimethoxyphenyl]lithium[9] Addition to 6. The lithium compound was obtained from the corresponding aromatic bromide by reaction with *t*-BuLi (2 equiv) and reacted essentially as described for the addition of methyllithium, the crude product was desilylated, and the quinol ether was purified by silica gel chromatography (1:1 Et_2O/PE as eluant) to give the pure quinol ether (65%) as an oil: IR (neat) 1670 (s), 1510 (s) cm^{-1}; ^1H NMR δ 6.95 (d, J_{AB} = 10.2 Hz, 2 H), 6.65 (s, 1 H), 6.36 (s, 1 H), 6.23 (d, J_{AB} = 10.2 Hz, 2 H), 4.09 (t, J = 5.4 Hz, 2 H), 3.87 (s, 3 H), 3.73 (s, 3 H), 2.87 (br t, J = 5.4 Hz, 2 H); mass spectrum, exact mass calcd for $C_{16}H_{16}O_4$ m/e 272.1048, obsd m/e 272.1051.

2-Bromo-4,5-dimethoxystyrene.[3] A THF solution of 6-bromoveratraldehyde (9.7 g, 0.0396 mol) was added to a THF (50 mL) solution of [(trimethylsilyl)methyl]magnesium chloride (0.044 mol) at 0 °C. The resulting mixture was stirred for 30 min and heated to reflux for 2 h. After cooling to room temperature, the reaction mixture was poured into saturated NH_4Cl (100 mL) and diluted with Et_2O (150 mL). The layers were shaken and separated, and the organic phase was washed with brine (2 × 50 mL), dried through $CaSO_4$, and concentrated in vacuo. The crude carbinol was then dissolved in THF (100 mL), NaH [1.84 g, 60% by weight in mineral oil; washed with hexane (2 × 5 mL)] was added, and the mixture was heated to reflux for 1 h. After cooling, the mixture was poured into cold H_2O (100 mL), Et_2O (100 mL) was added, and the layers were shaken and separated. The organic phase was washed with brine (50 mL) and was dried through $CaSO_4$. After the addition of hydroquinone (0.3 g), the product was concentrated in vacuo to afford the crude styrene (6.5 g, 68%) as a yellow oil, which was used without purification in the next step since the product underwent rapid polymerization during most purification attempts. A small portion was rapidly chromatographed on silica gel (6 in. × 0.25 in. column, hexane as eluant) to afford the analytically pure material as a waxy, white solid: mp 39–41 °C; IR (KBr) 1505 (s), 1260 (s), 1211 (s) cm^{-1}; ^1H NMR δ 7.2–6.8 (m, X component of ABX, partially obscured, 1 H), 7.04 (s, 1 H), 7.0 (s, 1 H), 5.58 [d, A component of ABX, further coupled ($J \simeq 1$ Hz), J_{AX} = 17 Hz, 1 H], 5.25 [d, B component of ABX, further coupled ($J \simeq 1$ Hz), J_{BX} = 11 Hz, 1 H], 3.90 (s, 3 H), 3.87 (s, 3 H); mass spectrum, exact mass calcd for $C_{10}H_{11}O_2Br$ m/e 241.9942, obsd m/e 241.9940.

Reaction of 2-Lithio-4,5-dimethoxystyrene with 6.[3] *n*-BuLi (7.0 mL of a 1.45 M solution) was added dropwise to a THF (30 mL) solution of 2-bromo-4,5-dimethoxystyrene (2.35 g, 9.7 mmol) at −78 °C. After being stirred for 2 h, a solution of **6** (2.5 g, 9.8 mmol) in THF (10 mL) was added dropwise, and the resulting mixture was stirred for 1 h at −78 °C and was allowed to warm to room temperature over 1 h. After quenching the reaction with saturated NH_4Cl (50 mL) and dilution with Et_2O (150 mL), the layers were separated. Workup gave an oil, which was dissolved in THF (150 mL) and treated with $(n\text{-}Bu)_4NF$ (4.0 g, 15 mmol) at 0 °C. After 30 min, the reaction mixture was poured into cold brine (150 mL), and Et_2O was added (200 mL). Workup gave an oil, which was chromatographed on silica gel (6 in. × 0.5 in. column, 1:1 EtOAc/hexane as eluant) to afford 4-hydroxy-4-(2-vinyl-4,5-dimethoxyphenyl)-2,5-cyclohexadienone (0.66 g, 25% overall) as a white solid, mp 154–158 °C. Recrystallization of a portion from Et_2O/hexane gave the analytical sample: mp 157–159 °C; IR (KBr) 1660 (s) cm^{-1}; ^1H NMR δ 7.25–6.90 (m, X component of ABX, partially obscured, 1 H), 7.23 (s, 1 H), 6.92 (s, 1 H), 6.94 (d, J_{AB} = 10.2 Hz, 2 H), 6.23 (d, J_{AB} = 10.2 Hz, 2 H), 5.4 (d, A component of ABX, further coupled ($J \simeq 1$ Hz), J_{AX} = 17 Hz, 1 H), 5.15 (d, B component of ABX, further coupled ($J \simeq 1$ Hz), J_{BX} = 11 Hz, 1 H), 3.88 (two overlapping singlets, 6 H), 2.34 (s, 1 H); mass spectrum, exact mass calcd for $C_{16}H_{16}O_4$ m/e 272.1049, obsd m/e 272.1058.

Formation and Hydrolysis of 1a.[3] An ether (1 mL) solution of 1-bromo-1-ethoxycyclopropane[8] (1.47 g, 8.1 mmol) was added

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via syringe to an Et_2O (25 mL) solution of *t*-BuLi (9 mL of a 1.7 M solution, 1.9 equiv) at −78 °C. After 15 min, 4,4-dimethoxycyclohexadienone (1.3 g, 8.1 mmol) was added, the resulting mixture was stirred for 1 h at −78 °C and then warmed to 0 °C with an ice bath, and the reaction was quenched with saturated NH_4Cl (5 mL). Workup as usual afforded a yellow oil whose NMR spectrum showed the formation of the expected quinol ketal. Without further purification, the crude product was dissolved in cold acetone (50 mL), 8% HOAc (10 mL) was added, and the mixture was stored overnight in the refrigerator. After 24 h, saturated $NaHCO_3$ (25 mL) was added, the acetone was removed in vacuo, and the product was extracted with Et_2O. Workup and concentration gave an orange oil, the ^1H NMR spectrum and TLC of which indicated the major product to be *p*-methoxyphenol.

Formation and Hydrolysis of 3.[3] *n*-BuLi (11.7 mL of a 1.6 M solution) was added over 5 min to a THF (30 mL) solution of 2-bromo-α-methylstyrene (3.4 g, 17 mmol) at −78 °C, and the resulting solution was stirred for 1 h. A solution of 4,4-dimethoxy-2,5-cyclohexadienone (2.6 g, 2.4 mL) in THF (5 mL) was added dropwise via syringe over 10 min, and the resulting brown solution was stirred for 1 h at −78 °C and then allowed to warm to room temperature. The reaction was quenched with saturated NH_4Cl (10 mL), and the mixture was diluted with Et_2O (150 mL). The layers were separated, and the organic phase was washed with brine (50 mL), dried through $CaSO_4$, and concentrated in vacuo. The crude *p*-quinol ketal was dissolved in THF (30 mL), Zn/Cu couple (3.0 g, 46 mmol) was added, and the mixture was brought to reflux with stirring while 5% HOAc (30 mL) was added dropwise. After being heated and stirred for 30 min, the reaction mixture was cooled to room temperature and was diluted with Et_2O (75 mL). The layers were separated, and the organic phase was washed with brine (2 × 50 mL), dried through $CaSO_4$, and concentrated in vacuo to afford a thick, oily semisolid (2.9 g), which was recrystallized from EtOAc/hexane to afford 4 (1.61 g, 42% overall from the styrene) as tan crystals: mp 115–117 °C; IR (KBr) 1241 (s) cm^{-1}; ^1H NMR δ 8.7–8.5 (structured m, 2 H), 8.1–8.0 (structured m, 1 H), 7.7–7.5 (structured m, 3 H), 7.3–7.2 (structured m, 2 H), 3.9 (s, 3 H), 2.7 (br s, 3 H); mass spectrum, exact mass calcd for $C_{16}H_{14}O$ *m/e* 222.1044, obsd *m/e* 222.1044.

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Asymmetric 1,3-Dipolar Cycloadditions of Nitrile Oxides Using Simple Chiral Auxiliaries[1]

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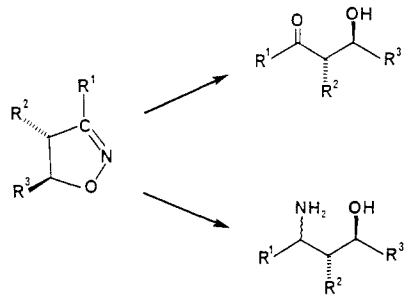
Dipolar cycloadditions of nitrile oxides to substituted bornyl crotonates give substituted isoxazolines with up to 80% diastereoselectivity. Both regioisomers of the adducts are produced in a ratio of approximately 3:1, independent of the substituent on the borneol and the nature of the nitrile oxide. The regioisomers, and sometimes the diastereomers, can be separated by flash chromatography. Reduction of the pure diastereomers with sodium borohydride yields enantiomerically pure 3-substituted 4-(hydroxymethyl)-5-methyl-2-isoxazolines.

A recent paper on the asymmetric induction in nitrile oxide cycloadditions[2] prompts us to report our results in this field. Substituted isoxazolines, resulting from 1,3-dipolar cycloadditions[3] of nitrile oxides[4] to 1,2-disubstituted olefins, are versatile intermediates for the synthesis of a wide variety of natural products.[5-7] Access to optically active isoxazolines would provide alternatives to the well-known asymmetric aldol reactions and, also, supply a new method for synthesizing enantiomerically pure primary amines (Scheme I).

Kozikowski et al. have examined the extent of diastereofacial selection in nitrile oxide additions due to an allylic asymmetric center in the dipolarophile[8] and the effects of chiral nitrile oxides.[9] Kametani and co-workers[10] have used menthyl esters and Curran et al.[2] have used menthyl and camphor sulfonamide derivatives to perform the cycloaddition reactions with chiral induction. Neither of these attempts provides a general method for diastereoselective 1,3-dipolar cycloadditions.

Scheme I. Alternative Routes from Chiral Isoxazolines



We have previously reported the use of substituted bornyl crotonates as chiral auxiliaries for conjugate additions of organocuprates[11] and now wish to report the successful use of these auxiliaries in diastereoselective cycloadditions of benzonitrile oxide and acetonitrile oxide.

Results and Discussion

The nitrile oxide additions to the bornyl crotonates 1 give four different cycloadducts; one pair of diastereomers for each regioisomer (Scheme II). The yields, regioselectivities, and diastereoselectivites of the reactions are presented in Table I.

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