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Catalytic Enantioselective Diels–Alder Reactions of 1,4-Quinone Monoketals

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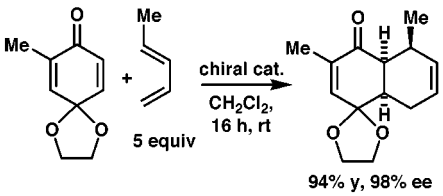
ABSTRACT



Achiral 1,4-quinone monoketals function well as dienophiles in enantioselective Diels–Alder reactions catalyzed by a chiral Ti(IV) Lewis acid.

For more than six decades the Diels−Alder reaction subtype involving quinones as dienophiles has provided a powerful construction for functionalized *cis*-fused decalin systems.[1] Many syntheses of complex natural products have been recorded in which the quinone Diels−Alder reaction has been used to set in place an initial arrangement of rings and stereocenters, paving the way for elaboration of the final target structure by a subsequent series of selective reactions. Examples include some of the most notable achievements in complicated synthetic chemistry, for instance: steroids,[2] reserpine,[3] ibogamine,[4] dendrobine,[5] gibberellic acid,[6] trichodermol,[7] and euonyminol.[8,9]

In each of these cases the initial Diels−Alder reaction generated a racemic adduct from which the synthesis of the chiral natural product was possible only with an intervening resolution step and the usual loss of material (>50%). At present, methodology is not available for conducting the key quinone Diels−Alder reactions for these syntheses under circumstances that would lead enantioselectively to chiral adducts. This gap in methodology has persisted despite the great progress that has been made in recent years in the development of enantioselective versions of other Diels−Alder subtypes involving chiral Lewis acid catalysts.[10] It seems likely that most of the chiral catalysts developed thus far for Diels−Alder reactions are ineffective for controlling enantioselection with quinones as dienophiles. In fact, only a few examples of such enantioselective reactions have appeared in the literature to our knowledge (see, e.g., Scheme 1).[11,12] The catalyst used was that derived from the reaction of (*R*)-BINOL with $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ in the presence of 4 Å

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(8) White, J. D.; Cutshall, N. S.; Kim, T. S.; Shin, H. *J. Am. Chem. Soc.* **1995**, *117*, 9780.
(9) For further examples of 1,4-quinone Diels−Alder reactions in natural product synthesis, see: (a) Bird, C. W.; Brown, A. L.; Chan, C. C.; Lewis, A. *Tetrahedron Lett.* **1989**, *30*, 6223. (b) Roush, W. R. *J. Am. Chem. Soc.* **1978**, *100*, 3599. (c) Oda, K.; Ichihara, A.; Sakamura, S. *Tetrahedron Lett.* **1975**, *16*, 3187. (d) Ichihara, A.; Oda, K.; Kobayashi, M.; Sakamura, S. *Tetrahedron Lett.* **1974**, *15*, 4235.

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(11) (a) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643. (b) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812. (c) White, J. D.; Choi, Y. *Org. Lett.* **2000**, *2*, 2373.
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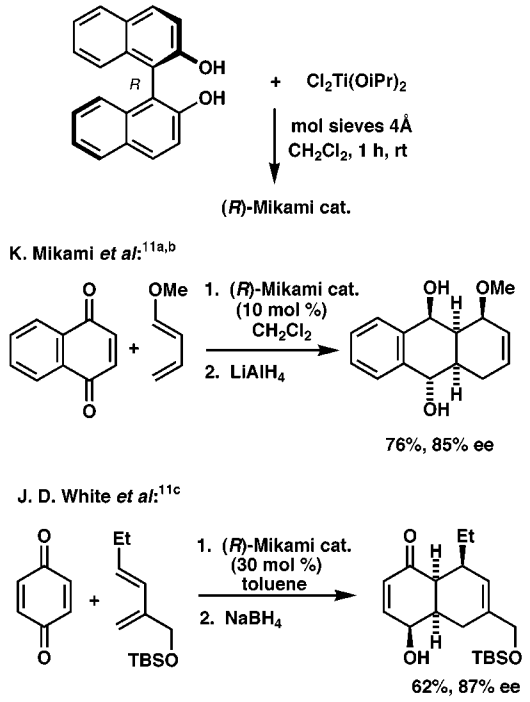
Scheme 1

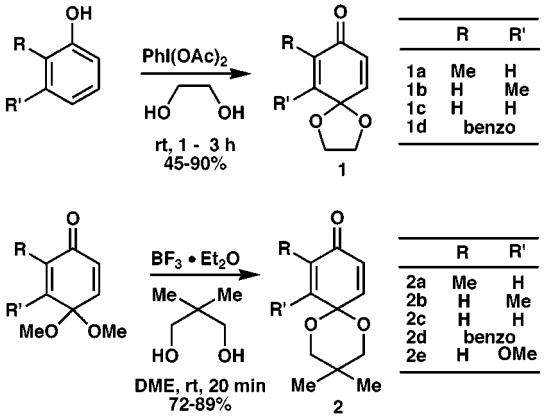


molecular sieves and H_2O (referred to herein as the Mikami catalyst).[13] The structure of the Mikami catalyst is unknown, but it appears to be chloride free and to involve μ-oxo bridges between at least two Ti units. The minimal structure would appear to be the μ_2-bridged possibility BINOL−Ti(μ_2O,μ_2O)-Ti−BINOL.

This Letter describes the results of our studies in this area using as substrates 1,4-quinone monoketals instead of quinones themselves. There are a number of potential advantages of 1,4-quinone monoketals (which are essentially 1,4-quinone equivalents) over the corresponding quinones, including the following: (1) the monoketals are expected to be more Lewis basic; (2) the monoketals would provide adducts that do not undergo facile aromatization, in contrast to the 1,4-quinone adducts which are known to be readily aromatized and difficult to handle (unless at least one of the 6,6-fusion substituents is a non-hydrogen angular group); (3) the monoketals provide adducts in which one of the two carbonyls of the 1,4-quinone is already protected, simplifying the task of further selective transformations; and (4) the monoketals are accessible synthetically either from oxidative *p*-ketalization of phenols or from transketalization starting from 4,4-dimethoxy-2,5-cyclohexadienones.

The ethylene glycol ketals **1a**,[13] **1b**,[14] **1c**,[15] and **1d**[16] can be prepared by literature procedures as shown in Scheme 2

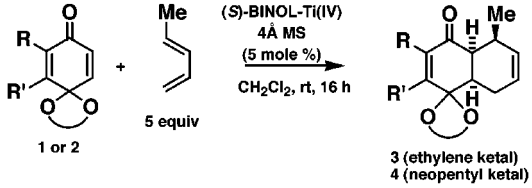
Scheme 2



using the reaction of the appropriate phenol with $PhI(OAc)_2$ in ethylene glycol.[17] The neopentyl glycol ketals **2** were prepared by BF_3-catalyzed transketalization starting with the appropriate 4,4-dimethoxy-2,5-cyclohexadienone and 2,2-dimethylpropane-1,3-diol.[18,19] Monoketal **2a** could also be prepared in 65% yield by oxidation of *o*-cresol with $PhI(OCOCF_3)_2$ in the presence of 10 equiv of 2,2-dimethylpropane-1,3-diol in CH_2Cl_2 solution at 23 °C for 30 min.

Initial studies of Diels−Alder reactions using the Mikami BINOL−Ti(IV) catalyst in CH_2Cl_2 at 23 °C with (*E*)-1,3-

Table 1. Enantioselective Diels−Alder Reactions of (*E*)-1,3-Pentadiene and 1,4-Quinone Monoketals **1** and **2** Catalyzed by the Mikami (*S*)-BINOL−Ti(IV)−Molecular Sieves System



1,4-quinone monoacetal	Diels-Alder product [a]	yield/ ee, %
1a	3a	97/98
1b	3b	92/96
1c	3c	86/84
1d	3d	95/92
2a	4a	90/99
2b	4b	94/87
2c	4c	97/93
2c	4c	95/87 [b]
2d	4d	93/95
2e	4e	91/98

[a] *endo/exo* ratios >99:1. [b] Toluene was used as solvent.

(13) Rose, P. A.; Lei, B.; Shaw, A. C.; Walker-Simmons, M. K.; Napper, S.; Quail, J. W.; Abrams, S. R. *Can. J. Chem.* **1996**, *74*, 1836.
(14) Pirrung, M. C.; Nunn, D. S. *Tetrahedron Lett.* **1992**, *33*, 6591.
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(16) Farina, F.; del Paredes, M. C.; Soto, J. J. *An. Quim.* **1995**, *91*, 50.
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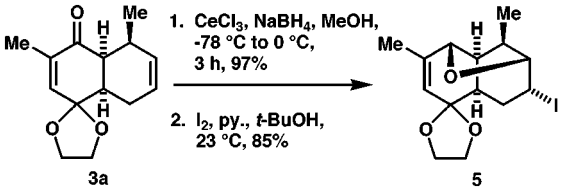
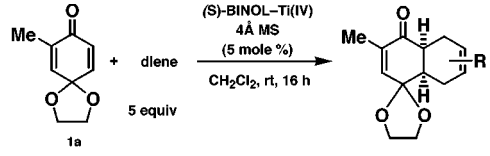
(18) Pirrung, M. C.; Nunn, D. S. *Tetrahedron* **1996**, *52*, 5707.
(19) (a) McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282. (b) Morrow, G. W.; Marks, T. M.; Sear, D. L. *Tetrahedron* **1995**, *51*, 10115. (c) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891.

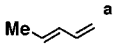
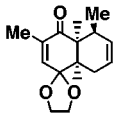
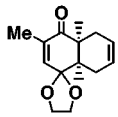
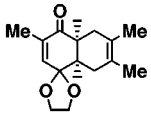
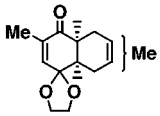
Scheme 3



pentadiene as the test diene and various 4,4-dimethoxy-2,5-cyclohexadienones were unpromising because of the marked instability of the adducts and difficulty of isolation. However, much better results were obtained with the ethylene monoketals **1** and the neopentyl monoketals **2**, as detailed in Table 1. The catalyst was prepared by stirring equimolar amounts of (*S*)-BINOL and $Cl_2Ti(O\textit{i}\text{-}Pr)_2$ in CH_2Cl_2 at 23 °C for 1 h in the presence of 4 Å molecular sieves (Aldrich, 5% H_2O content, 2−3 μm particle size, used as supplied), then the diene and dienophile were added, and the reaction was allowed to proceed at 23 °C for 16 h. Enantioselectivities were determined by HPLC analysis using an (*R*,*R*)-Whelk O1 column with hexane−*i*-PrOH (99:1) for elution. As the data in Table 1 show, very good yields, enantioselectivities, and *endo/exo* selectivities were obtained.[20] The use of 4 Å molecular sieves containing water was critical, in accordance with previous observations for catalytic ene reactions.[11,21,22]

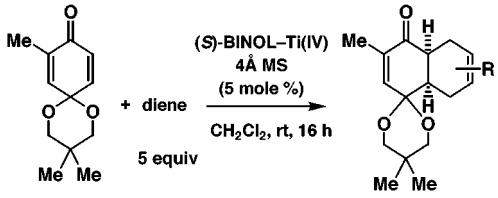
Table 2. Enantioselective Diels−Alder Reactions of Quinone Monoketal **1a** with Various Dienes Catalyzed by (*S*)-BINOL−Ti(IV)−4 Å Molecular Sieves

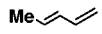
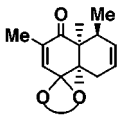
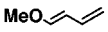
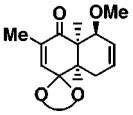
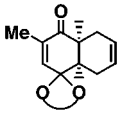
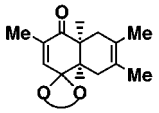
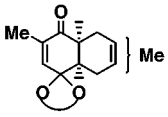


diene	product	yield/ ee, %
 [a]		97/98
 [b]		91/81
		88/84
		91/84, 72 [c]

[a] *endo/exo* ratio >98:2. [b] Reaction at −20 °C for 72 h. [c] Mixture of regioisomers (53:47).

Table 3. Enantioselective Diels−Alder Reactions of Quinone Monoketal **2a** with Various Dienes Catalyzed by (*S*)-BINOL−Ti(IV)−4 Å Molecular Sieves



diene	product	yield/ ee, %
		90/99
		90/99
 [b]		95/95
		95/90
		91/96, 91 [c]

[a] *endo/exo* >99:1. [b] Reaction at −20 °C for 72 h. [c] 56:44 mixture of regioisomers.

In the absence of molecular sieves or in the presence of molecular sieves that had been desiccated by heating to 150 °C under vacuum, the reactions were slower and less efficient. The assignment of absolute and relative configurations of the Diels−Alder adducts covered in Table 1 were made by analogy with the adduct **3a** from monoketal **1a**. The absolute structure of **3a** was proved by conversion to

(20) The following general procedure was followed for the Diels−Alder reactions shown in Table 1. To 4 Å molecular sieves (Aldrich 5−6% H_2O) was added a 0.02 M solution of (*S*)-2,2′-dihydroxy-1,1′-binaphthyl in CH_2Cl_2 (500 μL, 2.9 mg, 10 μmol) and a 0.30 M solution of $Cl_2Ti(OiPr)_2$ in toluene (33 μL, 10 μmol) at room temperature. The reddish brown reaction mixture was stirred for 1 h. A 0.50 M solution of the 1,4-quinone monoketal in CH_2Cl_2 (400 μL, 200 μmol) was added. After 10 min at 23 °C, the diene (5 equiv) was added and the reaction was stirred until TLC [deactivated silica gel (NEt_3), hexane:Et_2O 1:2] showed complete conversion. Column chromatography [deactivated silica gel (5% NEt_3), hexane:Et_2O 5:1→1:2] gave the analytically pure Diels−Alder adducts.

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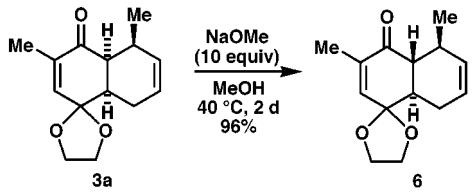
(23) The coordinates of **5** can be obtained on request from the Director, Cambridge, Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

the iodo ether **5**, mp 81 °C, as shown in Scheme 3, and X-ray crystallographic analysis of **5**.[23] It is interesting that the iodo ether **5** contains six stereocenters with all but one of the decalin carbons being functionalized or stereogenic.

We have also examined the catalytic enantioselective Diels−Alder reaction of monoketal **1a** with a series of dienes. The results are summarized in Table 2 for the (*S*)-Mikami catalyst (5 mol %) in CH_2Cl_2 at 23 °C. Enantioselectivities (81−84% ee) were found to be somewhat lower for butadiene and 2,3-dimethylbutadiene than for (*E*)-1,3-pentadiene (98%). In the case of the unsymmetrical diene isoprene, surprisingly poor regioselectivity (53:47) was observed, perhaps as a result of steric repulsion between the methyl group of isoprene and one of the ketal oxygens in the *endo* transition state corresponding to attachment of C(1) of 2-methylbutadiene to the enone β-carbon. These limitations prompted the examination of the corresponding Diels−Alder reactions with monoketal **2a**.

Table 3 sets forth the data on Diels−Alder reactions of the neopentyl monoketal **2a** with a number of dienes under the same conditions utilized for monoketal **1a** (Table 2). It is apparent that the neopentyl ketal **2a** affords substantially better results than does **1a**. However, regioselectivity is still a problem with isoprene as diene.

The catalytic enantioselective Diels−Alder reactions of 1,4-quinone monoketals described above provide a straightforward route to *trans*-decalins as well as *cis*-decalins. As shown below, methoxide-catalyzed epimerization under mild conditions converts the *cis*-decalone monoketal **3a** to the corresponding *trans*-fused ketone **6** in high yield, without the complication of aromatization which would operate with the 1,4-quinone adduct corresponding to **3a**.



The examples of catalytic enantioselective Diels−Alder reactions of 1,4-quinone monoketals with dienes which are summarized in Tables 1−3 clearly illustrate the potential of these reactions in the enantioselective synthesis of complex chiral organic molecules. Although the Mikami catalyst system is very useful in this connection, there is a clear need for the development of more clearly defined, more structurally homogeneous, and more efficacious catalysts. Work is in progress along these lines.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft for a postdoctoral fellowship to M.B. and Pfizer, Inc. for a research grant.

Supporting Information Available: Experimental procedures for the synthesis of monoketals and Diels−Alder adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

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