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Synthesis and Dienophilic Behavior of (*S*)-2-Cyano-3-(*p*-tolylsulfinyl)-1,4-benzoquinone

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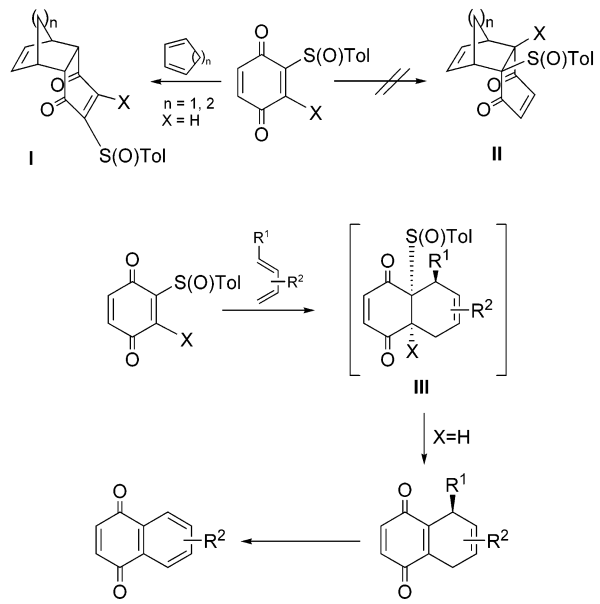
Abstract: Hydrocyanation of 2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**2**) followed by oxidation with $PhI(OAc)_2$ gives 2-cyano-3-(*p*-tolylsulfinyl)-1,4-benzoquinone (**1**). The generation of **1** in the presence of cyclic and acyclic dienes affords the Diels−Alder adducts with a complete chemo- (only reaction with the sulfinyl-substituted double bond takes place), regio- (controlled by the cyano group), and *endo* selectivity (with respect to the quinone moiety), whereas the π-facial selectivity is dependent on the structure of the diene.

The wide use of quinones as dienophiles[1] contrasts with their much lower applications in asymmetric Diels−Alder reactions. In this field, some studies of limited scope concerning the use of Ti,[2] B,[3] and other metal[4] complexes as chiral catalysts as well as other involving reactions with some chiral dienes[5] have been developed. The attachment of a chiral auxiliary to the quinone skeleton has also been investigated,[6] the best results being obtained with sulfinylquinones.[7] The complete endo selectivity and the high π-facial selectivity (strongly influenced by the reaction conditions) and reactivity are key features of the Diels−Alder reactions of these dienophiles.[7] Nevertheless, two main limitations exist when X = H (Scheme 1), concerning the impossibility to obtain adducts **II** with cyclic dienes and **III** with acyclic ones. Thus, the reaction of 2-(*p*-tolylsulfinyl)-1,4-benzoquinone with cyclic dienes affords with complete chemoselectivity

SCHEME 1



adducts **I**,[8] rather than adducts **II** resulting from the addition to the sulfinyl-substituted double bond. On the other hand, adducts **III** derived from acyclic dienes are very prone to desulfinylation and regenerate the quinonic structure under the reaction conditions.[8,9] Moreover, many of these quinones undergo subsequent aromatization, thus losing all the stereogenic centers created during the Diels−Alder reaction (Scheme 1).

To increase the scope of these attractive dienophiles, the search for sulfinylquinones able to evolve into types **II** and **III** adducts is undoubtably interesting. We reasoned that the presence of an electron-withdrawing group at C(3) could help to solve the above-mentioned problems. First, it would increase the reactivity of the C(2)−C(3) double bond, thus inverting the chemoselectivity and giving rise therefore to adducts **II** instead of **I**. Besides, desulfinylation from **III** would not be so favored, since the quinone structure cannot be recovered. The good results obtained in the Diels−Alder reactions of (*Z*)-*p*-tolylsulfinylacrylonitriles[10] and the easy introduction of a cyano into multiple bonds made it the group of choice. In this paper, we report the synthesis of (*S*)-2-cyano-3-(*p*-tolylsulfinyl)-1,4-benzoquinone (**1**, X = CN in Scheme

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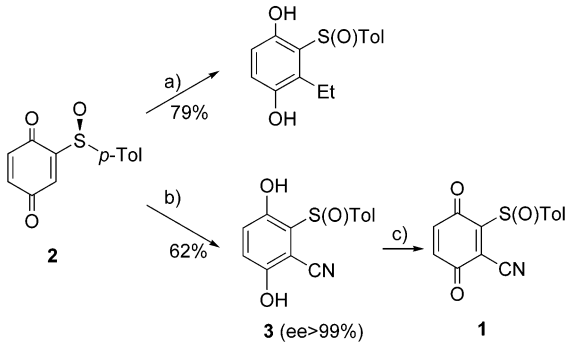
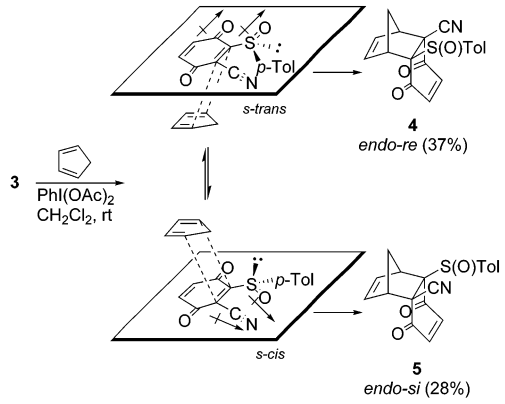
SCHEME 2[a]



[a] Reaction conditions: (a) Et_2AlCN/THF or toluene; (b) (i) $TMSCN/BF_3{\cdot}OEt_2$ (neat), (ii) NaOH (aq), (iii) HCl; (c) $PhI(OAc)_2$/acetone.

SCHEME 3



1) as well as its behavior as a dienophile in reactions with cyclopentadiene and 1-methoxybutadiene.

The synthesis of dienophile **1** was achieved through a two-step hydrocyanation−oxidation sequence starting from sulfinylquinone **2**.[11] The efficiency of Et_2AlCN in the hydrocyanation of vinylsulfoxides[12] prompted us to study its reaction with **2**. Surprisingly, when **2** was treated with Et_2AlCN in either THF or toluene, we observed the clean addition of an ethyl group instead of the expected cyanation (Scheme 2). Other hydrocyanating reagents[13] such as TMSCN/KCN/18-C-6 or LiCN were also unsuccessful. Finally, reaction of **2** with TMSCN in the presence of $BF_3{\cdot}OEt_2$ (40 mol %) and, importantly, under solvent-free conditions yielded the expected compound **3** (Scheme 2) along with its *O*-silyl derivative, making a basic workup necessary. After protonation and flash chromatography, cyanohydroquinone **3** was isolated in 62% yield and >99% ee (HPLC).

Next, we turned our attention to the oxidation of hydroquinone **3**. When the most usual reagents (CAN,[14] DDQ,[15] and AgO/HNO_3[16]) were employed, decomposition of the starting material occurred. The use of a hypervalent iodine reagent,[17] $PhI(OAc)_2$, gave identically poor results if the reaction was carried out in methanol. However, by tuning the solvent to acetone the formation of targeted quinone **1** could be observed, probably due to the non-nucleophilic character of this solvent (Scheme 2). The instability of this compound in solution precludes its chromatographic purification and makes more convenient the in situ generation of **1** in the presence of the diene.[18] Although the ee could not be established at this point (due to the low stability of **1**), it was accurately determined for the Diels−Alder adducts derived from **1** (vide infra).

When the reaction of hydroquinone **3** with $PhI(OAc)_2$ was immediately followed by addition of cyclopentadiene, a 57:43 mixture of two Diels−Alder adducts (**4** and **5**, Scheme 3) was obtained. From their ^1H NMR spectra it was easily deduced that cycloaddition had taken place to the sulfinyl-substituted double bond exclusively, showing that the extra-activation by the cyano group completely inverts the chemoselectivity typically observed in the reactions of quinone **2** with cyclopentadiene (see Scheme 1). The oxidation of the sulfinyl group of **4** and **5** afforded enantiomeric sulfones, evidencing both adducts result from the same *endo* or *exo* approach of the diene from different faces of the tetrasubstituted double bond. The enantiomeric purity (ee >99%) of the cycloadducts was established by chiral HPLC and their *endo* stereochemistry assumed on the basis of the well-established strong *endo*-director character of the quinone ring.[19]

All the attempts to improve the diastereoselection by changing the reaction conditions (solvent or temperature) were fruitless, a poor π-facial selectivity being observed in all cases. The best chemical yield was obtained when $PhI(OAc)_2$ was added over a mixture of hydroquinone **3** and cyclopentadiene in CH_2Cl_2 (65% overall yield (57:43 diastereomeric mixture) from **3,** Scheme 3).

The poor π-facial selectivity observed can be due to the existence of a similar population of both *s-cis* and *s-trans* conformers (the absence of a preferred conformation around the C−S bond must be a consequence of the strong dipolar interactions of the sulfinyl with both CN and CO groups destabilizing the *s-cis* and *s-trans* conformers, respectively). The preferred approach of the diene, governed by steric grounds, would take place from a different face in both conformations (that bearing the lone electronic pair at sulfur),[20] thus accounting for the

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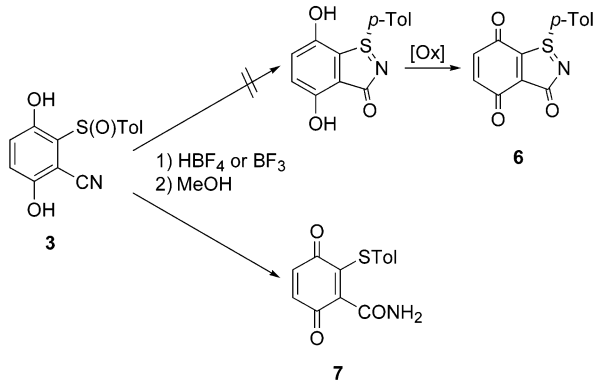
(18) Although the purification process is not always reproducible we could isolate a small amount of the pure quinone **1** by crystallization in acetone. The high specific rotation measured, [α] +1433 (*c* 0.26, acetone), suggested a high ee.

(19) The endo stereochemistry of the major adduct obtained in the reactions of **1** with 1-methoxybutadiene, whose structure was determined by X-ray diffraction (vide infra), also supports this assumption. Additionally, the sulfinyl and cyano groups in a *Z* arrangement do not have a very strong endo-directing character (see ref 10).

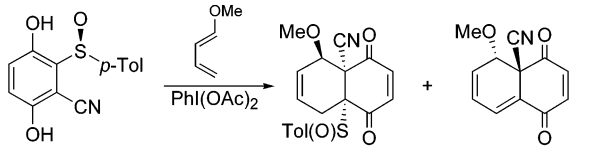
SCHEME 4



observed low facial selectivity (Scheme 3). According to this explanation, the formation of a chelated species by coordinating the sulfinyl and carbonyl oxygens with a metal atom appeared as a possible solution to improve the selectivity (it would favor the *s-trans* conformer). Unfortunately, the instability of the quinone in the presence of Lewis acids ($ZnBr_2$, $Eu(fod)_3$, or Me_2AlCl) made this strategy fail. We then tried to differentiate more efficiently the faces of **1** by its transformation into the rigid sulfimide **6**, supposedly achievable by treatment of **3** with HBF_4 or $BF_3{\cdot}OEt_2$[21] followed by oxidation of the resulting hydroquinone (Scheme 4). However, under such conditions **3** evolved into the achiral sulfide **7**.[22]

1-Methoxybutadiene was chosen as a model of acyclic diene. When we carried out its cycloaddition reaction with the cyanoquinone **1** under the optimal conditions found for cyclopentadiene, two compounds **8** and **9** were formed in an 86:14 ratio (entry 1, Table 1). As expected, none of the reaction products undergo aromatization. The structure of the major one was unambiguously established by X-ray analysis[23] as the adduct resulting from the *endo* addition of the diene to the *si* face of the dienophile. Compound **9** is a diene lacking the sulfinyl group, which must be formed by elimination of *p*-TolSOH from the corresponding Diels−Alder adduct. We concluded that **9** did not proceed from **8** since treatment of the latter under thermal, acidic or basic conditions did not afford **9** in any case. The regiochemistry was easily assigned from its ^{1}H NMR spectroscopic data and the results previously obtained from cyclopentadiene (only the two *endo* adducts were formed) suggested **9** must be derived from the other *endo* adduct.

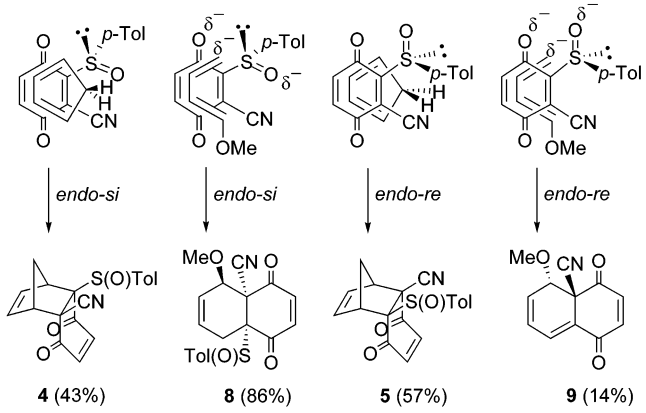
TABLE 1. Reactions of the Quinone 1 with 1-Methoxybutadiene under Different Conditions



entry	solvent	*T* (°C)	**8**/**9**[a]	ee[b] (%)
1	CH_2Cl_2	rt	86/14	85
2	CH_2Cl_2	0	88/12	92
3	acetone	0	79/21	88
4	CH_2Cl_2	−30	92/8	92

[a] By integration on the ^{1}H NMR spectrum of the crude reaction mixture. [b] Enantiomeric excess of **8** determined by HPLC.

SCHEME 5



These results indicate that the regioselectivity of the reaction is complete (it is controlled by the cyano group) as well as the *endo* selectivity (with respect to the quinone ring). The π-facial selectivity is much higher than that observed in the reaction with cyclopentadiene (84% vs 14% de). Taking into account that the conformational equilibrium of the dienophile is the same in both cases, interactions altering the energy of the different transition states must be invoked to explain this different behavior. In the cycloadditions with cyclopentadiene a steric interaction between the methylene bridge of the diene and the sulfinyl oxygen of the dienophile in the *s-cis* conformation could be responsible for the destabilization of the transition state corresponding to the *endo-si* addition (Scheme 5). This interaction is neither present on the *endo-re* addition (as it takes place on the *s-trans* conformer) nor with the acyclic diene due to the lack of methylene bridge. To explain the influence of the solvent polarity on the facial selectivity of reactions with 1-methoxybutadiene (compare entries 2 and 3 in Table 1) the existence of electrostatic repulsions destabilizing the endo-*re* approach, caused by the proximity of three negatively charged atoms (Scheme 5), can be invoked. This repulsion would be lower for the *endo-si* addition and would not exist in reactions with nonpolarized dienes (such as cyclopentadiene).

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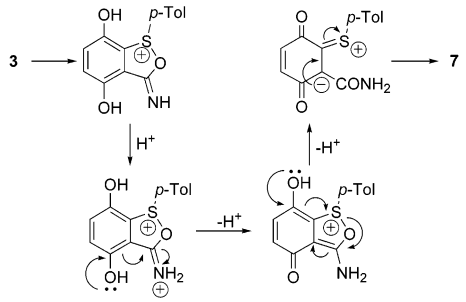
(22) This transformation could take place through the following mechanism:



(23) The authors have deposited atomic coordinates for **8** with the Cambridge Crystallographic Data Centre (Deposit No. 223619). The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

The enantiomeric excess of compound **8** obtained under the conditions of entry 1 (Table 1) is 85%. This loss of optical purity may be attributed to the lack of configurational stability of quinone **1**. It has been previously described[24] that (*Z*)-sulfinylacrylonitriles containing two additional electron-withdrawing groups present a low racemization barrier. This has been explained by assuming delocalization of the lone electronic pair at sulfur to the double bond when this is highly electron-deficient. In our case, the observed ee must be compromised by the relative rates of the racemization and the Diels−Alder reaction. The higher reactivity of cyclopentadiene compared to 1-methoxybutadiene accounts for the lower ee measured in the cycloadducts derived from the latter diene. The enantiomeric excess is slightly improved when the temperature decreases[25] (entries 2 and 4, Table 1), which also enhances the facial selectivity. Under optimal conditions (entry 4), the adduct **8** could be isolated in 71% yield and 92% ee, after flash chromatography.

In summary, we have demonstrated that the introduction of a cyano group at C(3) of 2(-*p*-tolylsulfinyl)-benzoquinone meets with change of chemoselectivity in the Diels−Alder reactions with cyclopentadiene and prevent the aromatization of the cycloadducts resulting from acyclic dienes. The problems derived from the low chemical and configurational stability of **1** can be minimized by its in situ generation in the presence of the diene. Regio- and endo-selectivity of the cycloadditions were found to be complete in all cases. The π-facial selectivity was dependent on the nature of the diene.

Experimental Section

(*S*)-3,6-Dihydroxy-2-(*p*-tolylsulfinyl)benzonitrile (3). To a mixture of TMSCN (3.1 mL, 23.2 mmol) and **2** (1.9 g, 7.72 mmol) under argon at 0 °C was added $BF_3{\cdot}OEt_2$ (392 μL, 3.1 mmol). It was stirred for 1 h at rt. Then, 15 mL of CH_2Cl_2 and 10 mL of 10% NaOH were added. After being stirred for 5 min, the aqueous layer was acidified by addition of concentrated HCl and extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were dried (Na_2SO_4), and the solvent was removed. Chromatographic purification (1:2 AcOEt−hexane) afforded **3** (1.31 g, 62%). The enantiomeric excess was found to be >99% (HPLC, Chiralpak AS, *i*-PrOH/hexane (30:70), 1.0 mL/min, 211 nm; (*S*)-**3** t_R = 9.7 min, (*R*)-**3** t_R = 19.6 min): $[\alpha]^{20}_D$ −116 (*c* 1.0, acetone); mp 136−137 °C (yellow solid); HRMS (EI) 273.0454, M^+ ($C_{14}H_{11}NO_3S$ requires 273.0460); IR (film) 3262, 2925, 2226, 1594, 1461, 1278, 1080 cm^{-1}; MS (EI) 273 (80) M^+, 257 (85), 225 (20), 139 (43), 92 (99.9), 91 (100), 77 (47), 65 (47);. ^1H NMR (CD_3COCD_3) δ 10.63 (bs, 1H), 9.92 (bs, 1H), 7.81 and 7.47 (AA′BB′ system, 4H), 7.13 and 7.05 (AB system, 2H, J = 9.1 Hz), 2.41 (s, 3H); ^{13}C NMR (CD_3COCD_3) δ 155.4, 153.2, 144.1, 140.8, 131.2 (2C), 126.6, 126.1 (2C), 125.0, 121.8, 113.8, 96.2, 21.3. Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.49; H, 4.15; N, 5.12; S, 12.02.

(*S*)-3,6-Dioxo-2-(*p*-tolylsulfinyl)cyclohexa-1,4-diene-1-carbonitrile (1). To a solution of **3** (55 mg, 0.20 mmol) in 500 μL of acetone was added $PhI(OAc)_2$ (71 mg, 0.22 mmol). A pure precipitate of **1** was filtered off: $[\alpha]^{20}_D$ +1433 (*c* 0.26, acetone); ^1H NMR (CD_3COCD_3) 7.80 and 7.43 (AA′BB′ system, 4H), 7.08 and 7.01 (AB system, 2H, J = 9.3 Hz), 2.41 (s, 3H); IR (film) 2925, 2232, 1667, 1594, 1454, 1237, 1140, 812 cm^{-1}.

General Procedure for One-Pot Hydroquinone Oxidation/Diels−Alder Reaction. To a mixture of **3** (55 mg, 0.20 mmol) and the diene (0.26 mmol) in 1 mL of CH_2Cl_2 was added $PhI(OAc)_2$ (71 mg, 0.22 mmol). After 20−40 min, the solvent was removed and the crude mixture purified by flash chromatography.

(1*R*,2*S*,7*S*,8*S*)-3,6-Dioxo-7-[(*S*)-*p*-tolylsulfinyl]tricyclo-[6.2.1.0^{2,7}]undeca-4,9-diene-2-carbonitrile (4). Oxidation of **3** followed by Diels−Alder reaction with cyclopentadiene at room temperature in CH_2Cl_2 afforded **4** in 37% yield after flash chromatography (1:4 acetone−hexane). The enantiomeric excess was found to be >99% (HPLC, Chiralpak AD, *i*-PrOH/hexane (30:70), 1.0 mL/min, 230 nm; **4** t_R = 11.0 min, *ent*-**4** t_R = 9.2 min): $[\alpha]^{20}_D$ −329 (*c* 0.94, $CHCl_3$); mp 107−108 °C (yellow solid; HRMS (FAB) 338.0860 $(M + 1)^+$ ($C_{19}H_{16}NO_3S$ requires 338.0851); MS (FAB) 338 (18) $(M + 1)^+$, 307 (30), 155 (30), 154 (100), 138 (36), 137 (64), 136 (72), 91 (18), 77 (27); ^1H NMR ($CDCl_3$) δ 7.72 and 7.29 (AA′BB′ system, 4H), 6.28 (dd, 1H, J = 3.1, 5.5 Hz), 6.26 and 6.00 (AB system, 2H, J = 10.4 Hz), 6.12 (dd, 1H, J = 3.0, 5.6 Hz), 4.20 (m, 1H), 4.05 (m, 1H), 2.46 (d, 1H, J = 10.1 Hz), 2.38 (s, 3H), 1.88 (dt, 1H, J = 10.8, 1.6 Hz).

(1*S*,2*R*,7*R*,8*R*)-3,6-Dioxo-7-[(*S*)-*p*-tolylsulfinyl]tricyclo-[6.2.1.0^{2,7}]undeca-4,9-diene-2-carbonitrile (5). Oxidation of **3** followed by Diels−Alder reaction with cyclopentadiene at room temperature in CH_2Cl_2 afforded **5** in 28% yield after flash chromatography (1:4 acetone−hexane). The enantiomeric excess was found to be >99% (HPLC, Chiralpak AD, *i*-PrOH/hexane (30:70), 1.0 mL/min, 230 nm; **5** t_R = 9.3 min, *ent*-**5** t_R = 10.4 min): $[\alpha]^{20}_D$ +539 (*c* 0.68, $CHCl_3$); mp 113−114 °C (yellow solid); HRMS (FAB) 338.0840 $(M + 1)^+$ ($C_{19}H_{16}NO_3S$ requires 338.0851); MS (FAB) 338 (24) $(M + 1)^+$, 272 (39), 139 (79), 95 (47), 91 (50), 81 (69), 73 (51), 69 (64), 57 (72), 55 (100); ^1H NMR ($CDCl_3$) δ 7.49 and 7.41 (AA′BB′ system, 4H), 6.77 and 6.68 (AB system, 2H, J = 10.4 Hz), 6.16 (dd, 1H, J = 2.9, 5.6 Hz), 6.01 (dd, 1H, J = 3.2, 5.5 Hz), 4.06 (m, 1H), 3.12 (m, 1H), 2.49 (s, 3H), 2.33 (d, 1H, J = 10.2), 1.80 (dt, 1H, J = 10.2, 1.7 Hz).

(4a*S*,5*R*,8a*R*)-1,4,4a,5,8,8a-Hexahydro-5-methoxy-1,4-dioxo-8a-[(*S*)-*p*-tolylsulfinyl]-1,4-naphthalene-4a-carbonitrile (8). Oxidation of **3** followed by Diels−Alder reaction with 1-methoxybutadiene at −30 °C in CH_2Cl_2 afforded **8** in 71% yield after flash chromatography (1:4 acetone−hexane). The enantiomeric excess was found to be 92% (HPLC, Chiralpak AD, *i*-PrOH/hexane (30:70), 1.0 mL/min, 230 nm; **8** t_R = 10.4 min, *ent*-**8** t_R = 14.3 min): $[\alpha]^{20}_D$ −220 (*c* 1.0, $CHCl_3$) for ee = 88%; mp 122−123 °C (yellow solid); HRMS (FAB) 356.0968 $(M + 1)^+$ ($C_{19}H_{18}NO_4S$ requires 356.0957); MS (FAB) 356 (28) $(M + 1)^+$, 217 (53), 216 (53), 154 (41), 139 (64), 136 (51), 107 (58), 95 (63), 91 (54), 81 (100), 55 (93); ^1H NMR ($CDCl_3$) δ 7.30 and 7.25 (AA′BB′ system, 4H), 7.09 and 6.64 (AB system, 2H, J = 10.4 Hz), 6.05 (m, 2H), 4.20 (m, 1H), 3.14 (s, 3H), 3.09 (ddd, 1H, J = 1.5, 4.1, 19.5 Hz), 2.59 (m, 1H), 2.39 (s, 3H).

(4a*S*,5*S*)-1,4,4a,5-Tetrahydro-5-methoxy-1,4-dioxo-1,4-naphthalene-4a-carbonitrile (9). Oxidation of **3** followed by Diels−Alder reaction with 1-methoxybutadiene at 0 °C in acetone afforded **9** in 21% yield and 88% ee after flash chromatography (1:4 acetone−hexane): $[\alpha]^{20}_D$ +442 (*c* 0.3, $CHCl_3$) for ee = 88%; mp 112−114 °C (yellow solid); HRMS (FAB) 216.0659 $(M + 1)^+$ ($C_{12}H_{10}NO_3$ requires 216.0661); MS (FAB) 216 (10) $(M + 1)^+$, 155 (32), 154 (100), 137 (74), 136 (80); ^1H NMR ($CDCl_3$) δ 7.37 (d, 1H, J = 5.4 Hz), 7.07 and 6.94 (AB system, 2H, J = 10.6 Hz), 6.72 (dd, 1H, J = 5.0, 9.5 Hz), 6.61 (dd, 1H, J = 5.4, 9.5 Hz), 4.42 (d, 1H, J = 5.0 Hz), 3.34 (s, 3H).

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Supporting Information Available: Copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**, **3**−**5**, **8**, and **9** and ORTEP structure of compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The racemization rate decreases when the temperature becomes lower. However, this also slows the Diels−Alder reaction, thus imposing a limit in the enhancement of the ee.