The Diels–Alder reactions of quinone imine ketals[1]

Scott C. Banfield and Michael A. Kerr

Abstract: *N*-Benzoyl- and *N*-arylsulfonyl-*p*-benzoquinone-mono-imine ketals (QIKs) undergo smooth Diels–Alder cycloadditions with typical 1,3-butadienes to yield the expected *endo* adducts. Treatment with catalytic acid rapidly converts the adducts to dihydronaphthalenes. The *N*-benzoyl derivatives require high pressures for cycloadditions while the *N*-tosyl and *N*-nosyl derivatives proceed under thermal (ambient pressure) conditions. In all cases the cycloadditions are completely regioselective.

Key words: Diels–Alder, quinone imine ketal, hyperbaric chemistry.

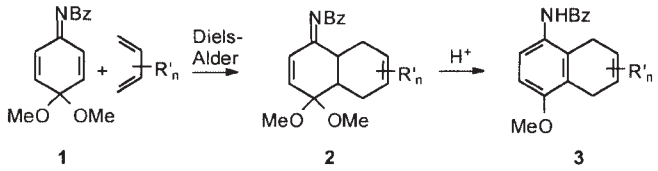
Résumé : Les cétals des *N*-benzoyl- et *N*-arylsulfonyl-*p*-benzoquinonemonoimines donnent facilement des réactions de cycloaddition de Diels–Alder avec les buta-1,3-dienes typiques et ils conduisent à la formation des adduits *endo* attendus. Le traitement avec une quantité catalytique d'acide provoque une transposition des adduits en dihydronaphtalènes. Les dérivés *N*-benzoylés nécessitent de hautes pressions pour donner les réactions de cycloaddition alors que les dérivés *N*-tosyl- et *N*-nosyl- se produisent à des conditions de température et de pression ambiantes. Dans tous les cas, les réactions de cycloadditions sont complètement diastéréosélectives.

Mots clés : Diels–Alder, cétal de la quinoneimine, chimie hyperbarique.

Introduction

The synthetic utility of the Diels–Alder reaction is questioned by no one. Its versatile ability to form a cyclohexene ring (with up to four new stereocenters) with exquisite control is well documented (1). So much work has been done to expand our understanding of this process over the years that one may now plan a complex synthesis involving a Diels–Alder reaction with a high degree of confidence for success. Even though the Diels–Alder reaction is a "mature reaction" in terms of its development, many opportunities exist to expand its utility. These include new dienophiles, dienes, and catalysts. Such developments allow the synthetic chemist the opportunity to tackle new and exciting challenges. Several years ago, we reported the participation of a benzoylated quinone imine ketal **1** in [4+2]-cycloadditions at ultra-high pressures (Scheme 1) (2). Prior to that work, the only report of such reactivity was made by Coutts et al. (3), in which several examples of sulphonylated quinone imine ketals as dienophiles were reported, although Swenton and coworkers (4) have explored the otherwise rich chemistry of benzoylated quinone imine ketals. The stable cycloadducts **2** could be isolated and purified or treated with acid to yield a dihydronaphthalene **3**. Subsequent to our initial report, we disclosed the synthesis of the tricyclic ergot skeleton using this reaction (5). This in turn inspired us to explore a general strategy for the synthesis of 5-methoxy indoles, which we recently reported in preliminary form (6). In the present paper we report the full details and an expanded scope of the hyperbaric Diels–Alder reactions of *N*-benzoyl quinone imine ketals, as well as a more generally usable and scalable thermal variant involving the *N*-arylsulphonyl counterparts.

Scheme 1.



Results and discussion

Synthesis of quinone imine ketals

The *N*-benzoyl quinone imine ketals **5a–d** were prepared by a simplification of the anodic oxidation method reported by Swenton et al. (4*a*) (Table 1). The oxidation is technically simple and is carried out in an open beaker on a stir plate with a platinum mesh electrode at a constant current of 0.3 A. Although other *N*-acyl derivatives (pivaloyl, acetyl, *tert*-butoxycarbonyl) were considered, the low reactivity of these compounds in a Diels–Alder sense, compared with the *N*-arylsulphonyl compounds (vide infra), led us to pursue the *N*-tosyl and *N*-nosyl derivatives instead.

While anodic oxidation yielded the desired products in the preparation of the *N*-arylsulphonyl QIKs, the yields were less than optimal and the reactions somewhat messy. We turned to oxidation with phenyliodo bis acetate (PIBA) (7). The preparation of QIKs by oxidation with this reagent has

Received 8 July 2003. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 9 January 2004.

This paper is dedicated to Ed Piers who continues to be an inspirational role model to so many.

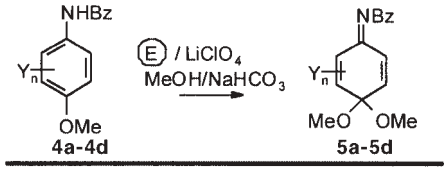
S.C. Banfield and M.A. Kerr.[2] Department of Chemistry, The University of Western Ontario, London, ON N6A 5B7, Canada.

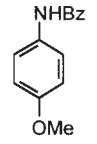
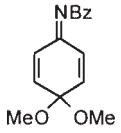
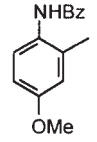
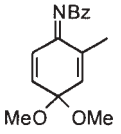
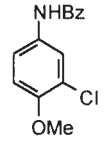
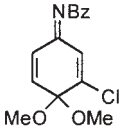
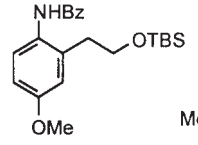
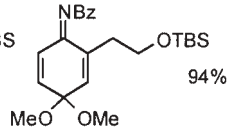
[1]This article is part of a Special Issue dedicated to Professor Ed Piers.

[2]Corresponding author (e-mail: makerr@uwo.ca).

 doi: 10.1139/V03-188

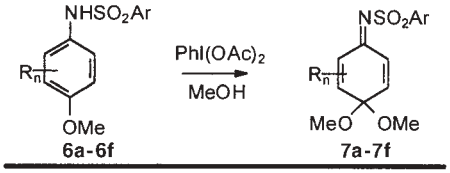
Table 1. Synthesis of *N*-benzoyl quinone imine ketals (QIK).

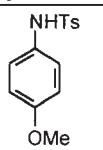
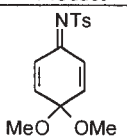
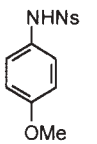
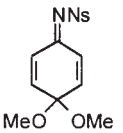
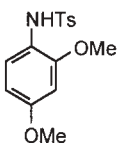
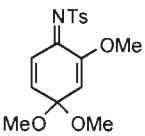
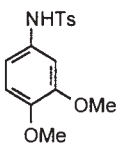
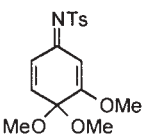
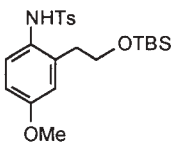
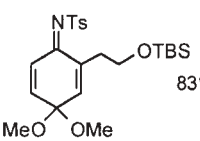
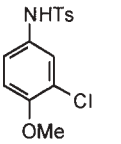
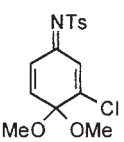


Entry	Anilide	Product	Yield
a			92%
b			96%
c			59%
d			94%

not been reported. Table 2 shows the results for the preparation of a series of *N*-arylsulphonyl QIKs **7a–f** by chemical oxidation of arylsulfonanilides **6a–f**.

Table 2. The synthesis of arylsulfonyl QIKs.



Entry	Anilide	Product	Yield
a			89%
b			74%
c			72%
d			87%
e			83%
f			81%

The Diels–Alder reactivity of QIKs

As expected, the removal of one carbonyl from conjugation with the dienophilic double bond greatly attenuates the dienophilicity of QIKs with respect to the parent *p*-benzoquinones. In fact, when QIKs **5** were subjected to reaction with a variety of 1,3-butadienes at elevated temperatures (150 °C), only decomposition was observed after 3 days. At this stage, high pressures were examined for several reasons, as follows: (*i*) The thermal activation ($\Delta H^{\ddagger}$) can be replaced by entropic activation ($\Delta V^{\ddagger}$) without the problem of thermal decomposition, and (*ii*) it is suspected that much of the low reactivity of these systems stems from the steric encumbrance imposed by the quaternary center adjacent to the reacting π-system, an encumbrance that can be overcome by the use of high pressures (8). In the case of the arylsulfonyl QIKs **7**, the increased electron-withdrawing ability of the tosyl or nosyl groups may overcome the inherent lack of reactivity, and a thermal process may be viable.

A key positive attribute of QIKs as dienophiles resides in the very properties that cause problems with reactivity. The presence of only one LUMO – lowering group on the reacting dienophilic π-bond imparts a degree of regioselectivity often missing in the parent quinones. In addition, the ketal moiety, which is restricted to be essentially orthogonal to the reacting π-systems, all but precludes the transition state A′ leading to the pseudo-*meta* regioisomer B′ (Fig. 1).

High pressure Diels–Alder reactions

The *N*-benzoyl QIK **5a** was subjected to reaction with a series of 5 dienes at 13 kbar (1 bar = 10^5 Pa) at ambient temperature[3] (Table 3). Typically, the reactions took about 7 days to proceed to completion and generally led to clean conversion to the *endo* cycloadducts.[4] These adducts are surprisingly stable to isolation and chromatography, although prolonged exposure to silica gel leads to small conversions to the aromatized species (vide infra). A consideration when using 2,3-dimethylbutadiene (entry d) is competitive polymerization of the diene. Use of a large excess of the diene often resulted in the solidification of the entire reaction mixture. This result is typical of our experiences using dienes that are unsubstituted at both termini of the diene moiety at elevated pressures. The fact that 1-*tert*-butyldimethylsilyloxy-1,3-butadiene (entry e) underwent reaction in higher

[3] This excludes the heating of the sample, which undoubtedly occurs upon compression of the high-pressure apparatus.
[4] The fact that these are *endo* adducts has been confirmed by NOESY experiments and has been published (ref. 2).

Fig. 1. Possible regiochemical outcomes for Diels–Alder reactions.

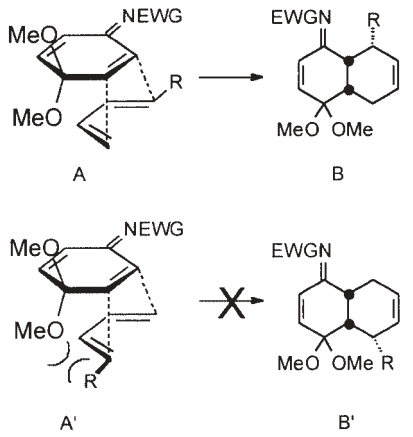
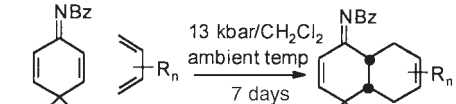
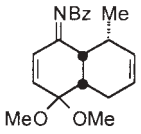
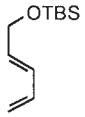
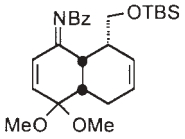
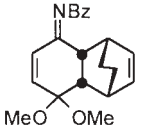
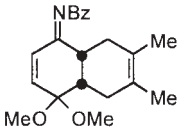
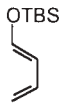
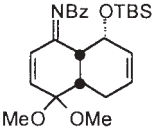


Table 3. Isolation of the initial adducts.



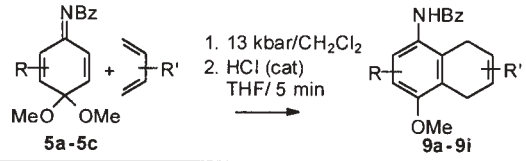
Entry	Diene	Product	Yield
a			89%
b			74%
c			72%
d			87%
e[a]			96%

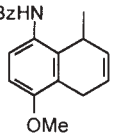
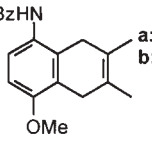
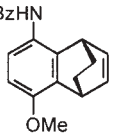
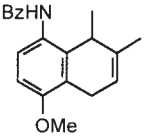
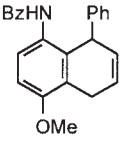
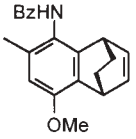
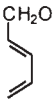
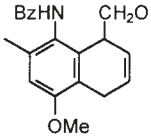
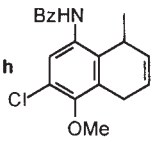
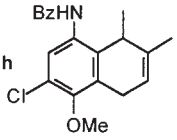
[a] Entry e had a reaction time of 3 days

yield and in less time is not surprising, since it is highly activated by the electron-donating silyloxy substituent.

Of interest to us for the synthesis of alkaloids was the fact that treatment of the adducts with a trace of acid effected the smooth aromatization to a dihydronaphthalene (i.e., **2**→**3** in Scheme 1). Table 4 shows the results of a series of reactions in which the initially formed adduct was isolated and the crude material treated with a drop of concentrated HCl in

Table 4. Hyperbaric Diels–Alder–aromatization results.



Entry	QIK	Diene	Conditions	Product	Yield
a	5a		a: 50 °C/12 h b: r.t/ 5 days		a: 97% b: 93%
b	5a		a: 50 °C/12 h b: r.t/ 7 days		a: 87% b: 91%
c	5a		a: 50 °C/12 h b: r.t/ 5 days		a: 92% b: 89%
d	5a		50 °C/12 h		81%
e	5a		r.t/ 7days		54%
f	5b		50 °C/12 h		92%
g	5b		50 °C/12 h		70%
h	5c		50 °C/12 h		85%
i	5c		50 °C/12 h		90%

THF to effect the formation of the dihydronaphthalene. It is important to note that for some cases in this series of reactions the temperature of the high-pressure reactor was raised

to 50 °C. This relatively minor increase in temperature reduced the reaction times from 7 days to 12 h.

The method of aromatization was also investigated. Mild acid sources such as silica gel were ineffective in promoting the transformation, while a mild Lewis acid such as ytterbium triflate resulted in decomposition. Use of *p*-toluenesulfonic acid resulted in the formation of desired product but also produced the free phenol, possibly because of hydrolysis by the water of hydration in the tosic acid.

Ambient pressure Diels–Alder reactions

In an attempt to make this reaction more widely applicable, we examined the Diels–Alder cycloadditions of *N*-tosyl and *N*-nosyl QIKs in the cycloadditions process. Replacement of the benzoyl moiety with the more electron-withdrawing aryl sulfonyl group should serve to enhance the dienophilicity of the QIK. To this end, **7a–c** and **7f** were heated in toluene with a series of 1,3-butadienes (Table 5). The *N*-tosyl QIKs underwent cycloadditions smoothly at 140 °C (sealed tube), while the more reactive nosyl derivatives required 100 °C as the reaction temperature. In most cases, a substantial amount of conversion to the dihydronaphthalene was observed. The aromatization was driven to completion by treatment with acid, as before, to yield the dihydronaphthalenes **10** in excellent yields. Other than the milder reaction temperatures, an advantage of using a nosyl group is the ease of removal of such a group from the adduct (9). On a larger scale, the reaction was performed in refluxing xylenes, using a standard reflux apparatus, and the aromatization was performed by addition of HCl directly to the xylenes solution. The dihydronaphthalene precipitated from the reaction mixture upon cooling with no significant reduction in chemical yield.

The cycloadducts themselves are suitable substrates for further oxidation and cycloadditions (Scheme 2). Adduct **10c** was hydrogenated to yield **11**, which could be oxidized as before in excellent yield to the QIK **12**. Cycloaddition of **12** with 3-methyl-1,3-pentadiene proceeded to give, after aromatization with catalytic HCl, the linear tricycle **13**.

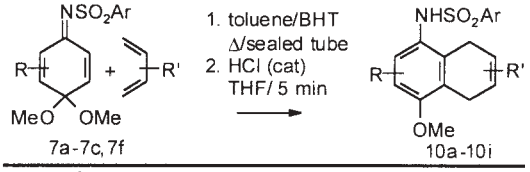
In summary, we have shown that quinone imine ketals bearing an electron-withdrawing group on the nitrogen atom are willing participants in hyperbaric or thermal Diels–Alder reactions. The adducts are readily aromatized with loss of methanol to produce dihydronaphthalenes in excellent yields. The synthetic utility of this process, including the conversion to 5-methoxyindoles, will be the subject of upcoming reports from our lab.

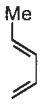
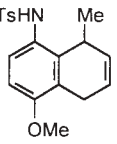
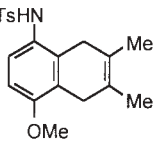
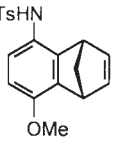
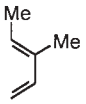
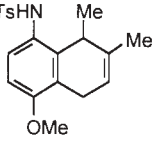
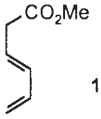
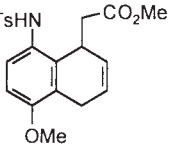
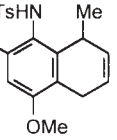
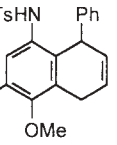
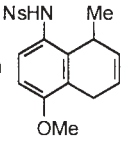
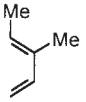
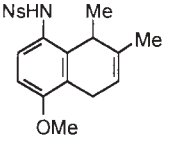
Experimental section

General considerations

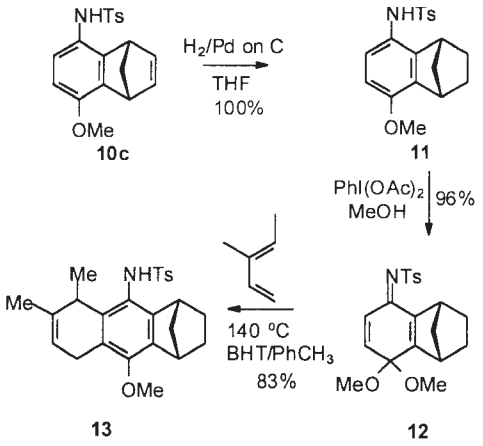
Infrared spectra were obtained as thin films on NaCl plates. NMR spectra were obtained at 600 or 400 MHz (^{1}H) and 150 or 100 MHz (^{13}C). Spectra were obtained in $CDCl_3$ (referenced at 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C) or DMSO-d_6 (referenced at 2.49 ppm for ^{1}H and 39.5 ppm for ^{13}C). Coupling values (J) are in Hz. EI Mass spectra were obtained at an ionizing voltage of 70 eV. Hyperbaric conditions were achieved using a LECO^{TM} Tempres high-pressure chemical reactor. Dichloromethane, toluene, and THF were distilled prior to use, according to the standard procedures

Table 5. Thermal Diels–Alder reactions of QIKs.



Entry	QIK	Diene	Conditions	Product	Yield
a	7a		140 °C/24 h		90%
b	7a		140 °C/24 h		88%
c	7a		140 °C/24 h		98%
d	7a		140 °C/24 h		96%
e	7a		140 °C/24 h		76%
f	7c		140 °C/24 h		85%
g	7f		140 °C/24 h		98%
h	7b		100 °C/7 h		99%
i	7b		100 °C/8 h		85%

Scheme 2.



(10). All other reagents were used as purchased from Aldrich or Lancaster and without purification. Reactions were checked for completion by TLC (EM Science, silica gel 60 F_{254}) and (or) ^{1}H NMR. Flash chromatography was performed using silica gel purchased from Silicycle Chemical Division Inc. (230–400 mesh). The synthesis of the *N*-benzoyl quinone imine ketals was carried out in the manner described by Swenton et al. (4*a*) with the only change being that the reaction was performed in an open beaker using a simple power source capable of producing a constant current of 0.3 A. The anode was a 2.5 cm × 5 cm Pt mesh cylinder, and the cathode was a 1 cm diameter Pt wire hoop. A simple laboratory power source was employed in the anodic oxidations. The Diels–Alder chemistry of the *N*-benzoyl quinone imine ketals has been described by us (2, 5, 6); however, a representative example for the preparation and Diels–Alder reaction of **5a** is given below.

General procedure for the preparation of *N*-benzoyl quinone imine ketals via anodic oxidation

Preparation of 5a

N-(4-Methoxyphenyl)benzamide (3.00 g, 13.2 mmol) was dissolved in 300 mL of a 2% solution of $LiClO_4$–CH_3OH. The mixture was cooled to 0 °C, and $NaHCO_3$ (6.00 g) was added. The mixture was rapidly stirred and anodically oxidized at a constant current (0.3 A) until consumption of the starting material was complete by TLC (approximately 140 min). The oxidation was stopped, and additional benzamide (2.62 g, 11.5 mmol) was added and allowed to dissolve, and the oxidation resumed until complete by TLC, approximately 140 min. The mixture was then poured into water and extracted several times with CH_2Cl_2. The combined organic layers were then washed with brine, dried (Na_2SO_4), filtered, and concentrated. The crude dienophile was then purified via flash chromatography (30%EtOAc–hexane) to yield 5.79 g (22.5 mmol, 91% yield) of the desired quinone imine ketal **5a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, *J* = 8.2 Hz, 2H), 7.60–7.56 (m, 1H), 7.48–7.44 (m, 2H), 6.57 (d, *J* = 9.0 Hz, 2H), 6.46 (d, *J* = 8.6 Hz, 2H), 3.34 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 180.3, 155.3, 139.6, 133.8, 132.9, 129.7, 128.9, 127.1, 93.2, 50.4. HR-MS (EI 70 eV) calcd. for $C_{15}H_{15}NO_3$: 257.1052; found: 257.1047.

General procedure for the high-pressure Diels–Alder reactions of *N*-benzoyl quinone imine ketals

Preparation of 8a and 9a

The quinone imine ketal **5a** (0.257 g, 1 mmol) was placed in a length (7″ (1″ = 25.4 mm)) of heat-shrinkable Teflon tubing. Dry CH_2Cl_2 (2 mL) was added, followed by an excess (0.5 mL) of technical grade piperylene. The tube was closed with a brass clamp and placed in the LECO^{TM} Tempres high-pressure chemical reactor. The pressure was raised to 13 kbar for a period of 7 days. The reaction mixture was poured directly onto a flash column of silica gel and eluted with 20% EtOAc in hexanes to produce 290 mg (90% yield) of a pure product, **8a**. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.89 (d, *J* = 7.5 Hz, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5, Hz, 2H), 6.09 (dd, *J* = 10.2, 2.1 Hz, 1H), 6.01 (d, *J* = 10.4 Hz, 1H), 5.71–5.68 (m, 2H), 3.28 (s, 3H), 3.25 (s, 3H), 3.27–3.22 (m, 1H), 2.72–2.64 (m, 2H), 2.20–1.88 (m, 2H), 1.48 (d, *J* = 7.6 Hz, 3H). ^{13}C NMR (63 MHz, $CDCl_3$) δ: 179.5, 164.7, 138.8, 133.4, 133.0, 132.9, 129.4, 128.5, 125.0, 123.8, 99.5, 49.7, 47.7, 43.7 (two signals), 35.0, 24.3, 18.7. IR (thin film) (cm^{-1}) ν: 3050, 3010, 2950, 2920, 2815, 1655, 1640, 1440, 1255. MS *m*/*z* (relative intensity): 326 (12, [M + 1]), 325 (48, $[M]^+$), 294 (15), 293 (21), 258 (43), 237 (20), 105 (100). HR-MS (EI 70 eV) calcd. for $C_{20}H_{23}NO_3$: 325.1678; found: 325.1687.

Preparation of 9a

The reaction performed, as for the preparation of **8a**, using **5a** (0.776 g, 3.0 mmol) and piperylene (0.613 g, 9.0 mmol) resulted in the formation of crude **8a**, which was taken up in 20 mL THF. Concentrated HCl (1 drop) was added, and the mixture was stirred for 30 min, after which time solid $NaHCO_3$ was added. The mixture was then stirred for an additional 10 min, and anhyd $MgSO_4$ was then added; stirring continued for 10 min further. The mixture was filtered, washed with THF, and concentrated. The crude residue was purified via trituration with cold hexanes; the solid was filtered and dried. The yield was 0.857 g (97%). ^{1}H NMR (400 MHz, DMSO) δ: 9.79 (s, 1H), 7.97 (app d, *J* = 6.8 Hz, 2H), 7.59–7.49 (m, 3H), 7.12 (d, *J* = 8.6 Hz, 1H), 6.85 (d, *J* = 8.6 Hz, 1Hz), 5.91–5.84 (m, 2H), 3.80 (s, 3H), 3.63–3.56 (m, 1H), 3.28–3.24 (m, 1H), 3.09–3.02 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ: 165.9, 154.8, 137.7, 134.6, 131.4, 130.6, 128.4, 127.7, 127.5, 127.0, 122.8, 122.7, 107.5, 55.4, 29.9, 24.0, 22.4. IR (thin films) ν: 3276, 1643. MS *m*/*z* (relative intensity): 294 (14, [M + 1]), 293 (66, $[M]^+$), 188 (21), 105 (100), 77 (43). HR-MS (EI 70 eV) calcd. for $C_{19}H_{19}NO_2$: 293.1416; found: 293.1409.

Typical procedure for the synthesis of *N*-arylsulfonyl quinone imine ketals

Preparation of 7a

In a 250 mL round-bottom flask, containing 125 mL of methanol, was dissolved 10.00 g (36 mmol) of **6a**. The solution was cooled to 0 °C; then 11.70 g (36 mmol) of diacetoxyiodobenzene was added portion-wise over 5 min. The flask was purged with argon and stirred until complete by TLC (approximately 30 min). The reaction mixture was then poured into water and extracted with EtOAc, then washed

successively with water, saturated $NaHCO_3$ (aq), and brine; then it was dried with $MgSO_4$, filtered, and concentrated. The crude product was then purified via recrystalization from CH_2Cl_2 to yield 9.87 g (32 mmol, 89% yield) of the product **7a** as a white solid. mp 109–111 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 7.81 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.36 (dd, J = 10.5, 2.2 Hz, 1H), 7.12 (dd, J = 10.5, 2.9 Hz, 1H), 7.01 (dd, J = 10.2, 2.9 Hz, 1H), 6.36 (dd, J = 10.2, 2.2 Hz, 1H), 3.28 (s, 6H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.8, 143.9, 143.2, 141.9, 137.4, 130.4, 129.4, 127.1, 123.0, 91.9, 50.3, 21.7. IR (thin film) (cm^{-1}) ν: 2835, 1555, 1321, 1156. MS *m/z* (relative intensity): 308 (3, [M + 1]), 307 (19, [M]$^+$), 276 (27), 152 (100), 139 (13), 121 (14), 91 (33). HR-MS (EI 70 eV) calcd. for $C_{15}H_{17}NO_4S$: 307.0878; found: 307.0879.

Quinone imine ketal (7b)

Oxidation of 11.10 g (36 mmol) of the nosylated *p*-anisidine **6b** with 11.62 g (36 mmol) of diacetoxyiodobenzene in 125 mL of methanol was performed in a similar manner to the preparation of compound **7a**, method A. The crude product was purified via a mixed recrystalization from EtOAc–MeOH to yield 9.00 g (26.6 mmol, 74% yield) of the product **7b** as an off-white solid. mp 132–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 and 8.18 (AA′BB′ system, 4H), 7.52 (dd, J = 10.5, 2.0 Hz, 1H), 6.87 (dd, J = 10.5, 2.7 Hz, 1H), 6.80 (dd, J = 10.2, 2.7 Hz, 1H), 6.34 (dd, J = 10.2, 2.0 Hz, 1H), 3.38 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.3, 150.2, 146.1, 144.7, 143.4, 129.9, 128.5, 124.1, 123.1, 91.7, 50.3. IR (thin film) (cm^{-1}) ν: 1532, 1326, 1154. MS *m/z* (relative intensity): 338 (5, [M]$^+$), 307 (46), 170 (14), 152 (100), 121 (28), 106 (17). HR-MS (EI 70 eV) calcd. for $C_{14}H_{14}N_2O_6S$: 338.0573; found: 338.0568.

Quinone imine ketal (7c)

Oxidation of 3.85 g (12.5 mmol) of the tosylated *p*-anisidine **6c** with 4.03 g (12.5 mmol) of diacetoxyiodobenzene in 50 mL of methanol was performed in a similar manner to the preparation of compound **7a**, method A. The crude product was purified via a recrystalization from CH_2Cl_2 to yield 3.05 g (9.0 mmol, 72% yield) of the product **7c** as a yellow solid. mp 137–140 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.80 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 10.5 Hz, 1H), 7.05 (dd, J = 10.5, 2.5 Hz, 1H), 5.98 (d, J = 2.5 Hz, 1H), 3.60 (s, 3H), 3.27 (s, 6H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1, 150.2, 144.7, 144.0, 137.3, 129.7, 126.7, 120.9, 111.6, 94.3, 55.3, 49.9, 21.1. IR (thin film) (cm^{-1}) ν: 2938, 1313, 1147. MS *m/z* (relative intensity): 338 (2, [M + 1]), 337 (10, [M]$^+$), 306 (100), 182 (51), 151 (43), 91 (35). HR-MS (EI 70 eV) calcd. for $C_{16}H_{19}NO_5S$: 337.0984; found: 337.0992.

Quinone imine ketal (7d)

Oxidation of 5.00 g (16.3 mmol) of the tosylated *p*-anisidine **6d** with 5.25 g (16.3 mmol) of diacetoxyiodobenzene in 50 mL of methanol was performed in a similar manner to the preparation of compound **7a**, method A. The crude product was purified via recrystalization from CH_2Cl_2 to yield 4.74 g (14.1 mmol, 87% yield) of the product **7d** as a yellow solid and as a (1.8:1) mixture of *trans*- and *cis*-isomers, respectively. mp 110–112 °C. ^{1}H NMR (400 MHz, DMSO-d_6, *trans*-isomer) δ: 7.79 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 6.79 (d, J = 10.2 Hz, 1H), 6.62 (d, J = 1.6 Hz, 1H), 6.36 (dd, J = 10.2, 1.6 Hz, 1H), 3.85 (s, 3H), 3.20 (s, 6H), 2.39 (s, 3H). ^{1}H NMR (400 MHz, DMSO-d_6, *cis*-isomer) δ: 7.79 (obscured by aryl sulfonyl, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.42 (obscured by aryl sulfonyl, 1H), 6.89 (d, J = 10.2 Hz, 1H), 5.77 (m, 1H), 3.79 (s, 3H), 3.20 (s, 6H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, both isomers) δ: 170.7, 169.4, 166.3, 165.5, 143.7, 143.6, 142.8, 141.1, 138.4, 138.1, 130.7, 129.7 (two overlapping signals), 126.7, 126.6, 122.8, 102.7, 96.4, 92.7, 92.6, 56.6, 56.5, 50.8 (two overlapping signals), 21.0 (two overlapping signals). IR (thin film) (cm^{-1}) ν: 2835, 1596, 1302, 1146. MS *m/z* (relative intensity): 338 (2, [M + 1]), 337 (9, [M]$^+$), 306 (36), 182 (100), 151 (8), 91 (24). HR-MS (EI 70 eV) calcd. for $C_{16}H_{19}NO_5S$: 337.0984; found: 337.0989.

Quinone imine ketal (7f)

Oxidation of 2.00 g (6.4 mmol) of the tosylated *p*-anisidine **6f** with 2.07 g (6.4 mmol) of diacetoxyiodobenzene in 20 mL of methanol was performed in a similar manner to the preparation of compound **7a**, method B. Filtration and washing with hexanes yielded 1.78 g (5.2 mmol, 81% yield) of the product **7f** as a yellow solid and as a (1.1:1) mixture of *cis*- and *trans*-isomers, respectively. No further purification was required. mp 100–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6, *trans*-isomer) δ: 7.82 (d, J = 8.4 Hz, 2H), 7.57 (dd, J = 10.4, 2.0 Hz, 1H), 7.47–7.45 (m, 2H), 7.18 (d, J = 10.4 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H), 3.20 (s, 6H), 2.41 (s, 3H). ^{1}H NMR (400 MHz, DMSO-d_6, *cis*-isomer) δ: 7.83 (d, J = 8.4 Hz, 2H), 7.72 (d, J = 2.1 Hz, 1H), 7.47–7.45 (m, 2H), 7.10 (d, J = 10.3 Hz, 1H), 6.60 (dd, J = 10.3, 2.1 Hz, 1H), 3.20 (s, 6H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, both isomers) δ: 161.8, 160.9, 152.8, 149.7, 144.2, 144.1, 143.5, 142.2, 137.1, 137.0, 132.6, 131.6, 129.5 (two overlapping signals), 127.2, 127.1, 125.1, 124.7, 94.34, 94.31, 51.61, 51.58, 21.7 (two overlapping signals). IR (thin film) (cm^{-1}) ν: 2924, 2837, 1320, 1156. MS *m/z* (relative intensity): 343 (9, [M + 2]), 342 (6, [M + 1]), 341 (23, [M]$^+$), 310 (45), 306 (32), 186 (100), 139 (23), 91 (92). HR-MS (EI 70 eV) calcd. for $C_{15}H_{16}ClNO_4S$: 341.0489; found: 341.0494.

Typical procedure for the thermal Diels–Alder–aromatization reactions of quinone imine ketals

Preparation of dihydronaphthalene (10a)

The quinone imine ketal **7a** (0.503 g, 1.6 mmol) and piperylene (0.393 g, 5.8 mmol) were taken up in dry toluene (2.3 mL) in an oven-dried sealed tube. One crystal of the radical inhibitor BHT was added, and the tube was flushed with argon before sealing. The reaction mixture was heated at 140 °C for a period of 24 h, after which time the reaction mixture was concentrated and taken up in dry THF (20 mL). Concentrated HCl (2 drops) was added, and the mixture was stirred under argon for 30 min, after which time solid $NaHCO_3$ was added. The mixture was then stirred for an additional 10 min, and anhyd $MgSO_4$ was then added; stirring continued for 10 min further. The mixture was filtered, washed with THF, and concentrated. The crude residue was purified via trituration with cold hexane; the solid was fil-

tered and dried to yield 0.509 g (1.48 mmol, 90% yield) of the product **10a** as a white solid. mp 152–156 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.23 (s, 1H), 7.58 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 6.60 (d, J = 8.7 Hz, 1H), 6.36 (d, J = 8.7 Hz, 1H), 5.90–5.79 (m, 2H), 3.81–3.71 (m, 1H), 3.69 (s, 3H), 3.27–3.20 (m, 1H), 2.99–2.93 (m, 1H), 2.38 (s, 3H), 1.06 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.4, 143.5, 137.7, 136.7, 130.2, 129.5, 127.2, 125.4, 124.9, 124.3, 123.0, 107.2, 55.3, 29.7, 24.2, 22.5, 21.5. IR (thin film) (cm^{-1}) ν: 3244, 1484, 1160. MS *m/z* (relative intensity): 344 (17, [M + 1]), 343 (73, [M]$^+$), 277 (7), 188 (100), 92 (6), 91 (24). HR-MS (EI 70 eV) calcd. for $C_{19}H_{21}NO_3S$: 343.1242; found: 343.1245.

Dihydronaphthalene (10b)

The reaction between quinone imine ketal **7a** (0.504 g, 1.6 mmol) and 2,3-dimethyl-1,3-butadiene (0.509 g, 5.7 mmol) was performed in a similar manner to the preparation of compound **10a**. The crude residue was purified via trituration with cold hexane; the solid was filtered and dried to yield 0.506 g (1.41 mmol, 88% yield) of the product **10b** as a white solid. mp 172–175 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.21 (s, 1H), 7.54 (d, J = 8.3 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 6.67–6.61 (m, 2H), 3.71 (s, 3H), 3.02–2.97 (m, 4H), 2.36 (s, 3H), 1.66 (s, 3H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 154.7, 142.7, 138.1, 133.3, 129.5, 126.7, 126.0, 125.5, 123.4, 122.0, 121.8, 107.2, 55.2, 32.1, 30.8, 20.9, 18.2 (two overlapping signals). IR (thin film) (cm^{-1}) ν: 3274, 1486, 1161. MS *m/z* (relative intensity): 358 (16, [M + 1]), 357 (66, [M]$^+$), 202 (3), 186 (100), 171 (23), 91 (18). HR-MS (EI 70 eV) calcd. for $C_{20}H_{23}NO_3S$: 357.1399; found: 357.1406.

Dihydronaphthalene (10c)

The reaction between quinone imine ketal **7a** (1.00 g, 3.25 mmol) and cyclopentadiene (0.98 mL, 11.8 mmol) was performed in a similar manner to the preparation of compound **10a**. The crude residue was purified via trituration with cold hexane; the solid was filtered and dried to yield 1.082 g (3.17 mmol, 98% yield) of the product **10c** as an off-white solid. mp 137–140 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.51 (s, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 6.65 (dd, J = 5.2, 3.0 Hz, 1H), 6.58 (d, J = 8.8 Hz, 1H), 6.51 (d, J = 8.8 Hz, 1H), 6.26 (dd, J = 5.2, 3.0 Hz, 1H), 3.94 (br s, 1H), 3.76 (br s, 1H), 3.68 (s, 3H), 2.33 (s, 3H), 1.90 (d, J = 7.0 Hz, 1H), 1.67 (d, J = 7.0 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6) δ: 151.6, 149.4, 142.8, 142.7, 142.2, 138.1, 137.1, 129.4, 126.8, 124.1, 123.8, 109.3, 68.8, 55.3, 48.0, 46.2, 20.9. IR (thin film) (cm^{-1}) ν: 3260, 1490, 1161. MS *m/z* (relative intensity): 342 (11, [M + 1]), 341 (43, [M]$^+$), 186 (100), 160 (13), 91 (25). HR-MS (EI 70 eV) calcd. for $C_{19}H_{19}NO_3S$: 341.1086; found: 341.1081.

Dihydronaphthalene (10d)

The reaction between quinone imine ketal **7a** (0.508 g, 1.65 mmol) and 3-methyl-1,3-pentadiene (0.471 g, 5.7 mmol) was performed in a similar manner to the preparation of compound **10a**. The crude residue was purified via trituration with cold hexane; the solid was filtered and dried to yield 0.563 g (1.58 mmol, 96% yield) of the product **10d** as a white solid. mp 160–162 °C. ^{1}H NMR (400 MHz, DMSO) δ: 9.24 (s, 1H), 7.55 (app d, J = 8.3 Hz, 2H), 7.35 (app d, J = 8.3 Hz, 2H), 6.62 (d, J = 8.7 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 5.51–5.50 (m, 1H), 3.70 (s, 3H), 3.45–3.41 (m, 1H), 3.24 (dd, J = 21.6, 5.4 Hz, 1H), 2.89 (dd, J = 21.6, 2.3 Hz, 1H), 2.37 (s, 3H), 1.67 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO) δ: 154.7, 142.5, 140.3, 137.9, 137.1, 129.3, 126.5, 126.0, 125.3, 123.3, 117.8, 107.1, 55.3, 34.1, 24.3, 21.2, 21.0, 20.4. IR (thin film) (cm^{-1}) ν: 3279, 1486, 1161. MS *m/z* (relative intensity): 358 (15, [M + 1]), 357 (62, [M]$^+$), 202 (100), 187 (45), 172 (18), 91 (12). HR-MS (EI 70 eV) calcd. for $C_{20}H_{23}NO_3S$: 357.1399; found: 357.1402.

Dihydronaphthalene (10e)

The reaction between quinone imine ketal **7a** (0.304 g, 0.99 mmol) and methyl (*E*)-3,5-hexadienoate (0.442 g, 3.5 mmol) was performed in a similar manner to the preparation of compound **10a**. The crude residue was purified via flash chromatography (40% EtOAc–hexane) to yield 0.303 g (0.75 mmol, 76% yield) of the product **10e** as a white solid. mp 124–127 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.31 (s, 1H), 7.57 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.2 Hz, 2H), 6.65 (d, J = 8.7 Hz, 1H), 6.42 (d, J = 8.7 Hz, 1H), 5.95–5.87 (m, 2H), 4.18–4.14 (m, 1H), 3.70 (s, 3H), 3.59 (s, 3H), 3.29–3.22 (m, 1H), 3.00–2.94 (m, 1H), 2.65 (dd, J = 15.4, 3.8 Hz, 1H), 2.38 (s, 3H), 2.14 (dd, J = 15.4, 10.5 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 171.5, 155.1, 142.8, 137.9, 137.2, 129.6, 127.8, 126.8, 126.3, 125.8, 125.4, 124.5, 107.8, 55.4, 51.3, 40.5, 31.2, 24.1, 21.0. IR (thin film) (cm^{-1}) ν: 3255, 1735, 1485, 1161. MS *m/z* (relative intensity): 402 (8, [M + 1]), 401 (30, [M]$^+$), 327 (31), 246 (18), 186 (84), 172 (100), 91 (28). HR-MS (EI 70 eV) calcd. for $C_{21}H_{23}NO_5S$: 401.1297; found: 401.1292.

Dihydronaphthalene (10f)

The reaction between quinone imine ketal **7c** (0.501 g, 1.49 mmol) and piperylene (0.357 g, 5.2 mmol) was performed in a similar manner to the preparation of compound **10a**. The crude residue was purified via trituration with cold hexane; the solid was filtered and dried to yield 0.472 g (1.26 mmol, 85% yield) of the product **10f** as an off-white solid. mp 210–213 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.90 (s, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 6.30 (s, 3H), 5.89–5.80 (m, 2H), 3.96–3.95 (m, 1H), 3.75 (s, 3H), 3.23–3.10 (m, 1H), 3.05 (s, 3H), 2.96–2.93 (m, 1H), 2.37 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 156.1, 155.2, 141.9, 141.8, 139.4, 130.8, 128.7, 126.7, 122.6, 114.1, 113.7, 92.9, 55.4, 54.5, 29.8, 23.7, 22.5, 20.9. IR (thin film) (cm^{-1}) ν: 3239, 1591, 1160. MS *m/z* (relative intensity): 374 (6, [M + 1]), 373 (15, [M]$^+$), 218 (100), 186 (18), 91 (16). HR-MS (EI 70 eV) calcd. for $C_{20}H_{23}NO_4S$: 373.1348; found: 373.1352.

Dihydronaphthalene (10g)

The reaction between quinone imine ketal **7f** (0.500 g, 1.46 mmol) and 1-phenyl-1,3-butadiene (0.686 g, 5.27 mmol) was performed in a similar manner to the preparation of compound **10a**. The crude residue was purified via trituration with cold hexane; the solid was filtered and dried to yield 0.631 g (1.43 mmol, 98% yield) of the product **10g**

as a white solid. mp 152–155 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.17 (s, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 7.23 (dd, J = 7.4, 7.2 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H), 7.06 (d, J = 7.2 Hz, 2H), 6.37 (s, 1H), 5.96–5.88 (m, 2H), 5.19–5.18 (m, 1H), 3.77 (s, 3H), 3.45–3.44 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 151.4, 144.5, 143.2, 136.5, 135.9, 131.5, 131.1, 129.5, 129.3, 128.4, 127.9, 127.0, 126.0, 124.9, 123.7, 121.8, 60.0, 40.9, 24.9, 21.0. IR (thin film) (cm^{-1}) ν: 3329, 1161. MS *m*/*z* (relative intensity): 440 (12, [M + 1]), 439 (40, [M]$^+$), 311 (16), 284 (100), 249 (45), 234 (30), 130 (42), 91 (78). HR-MS (EI 70 eV) calcd. for $C_{24}H_{22}ClNO_3S$: 439.1009; found: 439.1005.

Dihydronaphthalene (10h)

The quinone imine ketal **7b** (0.511 g, 1.51 mmol) and piperylene were taken up in dry toluene (2.3 mL) in an oven-dried sealed tube. One crystal of the radical inhibitor BHT was added, and the tube was flushed with argon before sealing. The reaction mixture was heated at 100 °C for a period of 7 h, after which time the reaction mixture was concentrated and taken up in dry THF (20 mL). Concentrated HCl (2 drops) was added, and the mixture was stirred under argon for 30 min, after which time solid $NaHCO_3$ was added. The mixture was then stirred for an additional 10 min, and anhyd $MgSO_4$ was then added, stirring for 10 min further. The mixture was then filtered, washed with reagent grade THF, and concentrated. The crude residue was purified via trituration with cold hexane; the solid was filtered and dried to yield 0.564 g (1.50 mmol, 99% yield) of the product **10h** as a white solid. mp 193–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.74 (s, 1H), 8.41 (d, J = 8.8 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 8.7 Hz, 1H), 6.35 (d, J = 8.7 Hz, 1H), 5.90–5.75 (m, 2H), 3.78–3.76 (m, 1H), 3.70 (s, 3H), 3.27–3.22 (m, 1H), 3.00–2.94 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.5, 149.6, 146.4, 140.1, 130.7, 128.4, 126.3, 125.2, 124.6, 123.8, 122.8, 107.4, 55.3, 29.6, 24.0, 22.4. IR (thin film) (cm^{-1}) ν: 3275, 1588, 1532, 1349, 1167. MS *m*/*z* (relative intensity): 375 (11, [M + 1]), 374 (49, [M]$^+$), 188 (100), 173 (32), 122 (10). HR-MS (EI 70 eV) calcd. for $C_{18}H_{18}N_2O_5S$: 374.0936; found: 374.0940.

Dihydronaphthalene (10i)

The quinone imine ketal **7b** (0.500 g, 1.48 mmol) and 3-methyl-1,3-pentadiene (0.447 g, 5.44 mmol) were taken up in dry toluene (2.3 mL) in an oven-dried sealed tube. One crystal of the radical inhibitor BHT was added, and the tube was flushed with argon before sealing. The reaction mixture was heated at 100 °C for a period of 8 h, at which point NMR analysis revealed 100% conversion to the desired dihydronaphthalene **10i**. The reaction mixture was concentrated, and the crude residue was purified via trituration with cold hexane to yield 0.487 g (1.25 mmol, 85% yield) of the product **10i** as a yellow solid. mp 166–169 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.75 (s, 1H), 8.41 (d, J = 8.9 Hz, 2H), 7.92 (d, J = 8.9 Hz, 2H), 6.63 (d, J = 8.8 Hz, 1H), 6.46 (d, J = 8.8 Hz, 1H), 5.53–5.52 (m, 1H), 3.70 (s, 3H), 3.44–3.43 (m, 1H), 3.28–3.21 (m, 1H), 2.94–2.88 (m, 1H), 1.67 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ: 155.3, 149.6, 146.4, 140.7, 137.1, 128.4, 126.4, 124.7, 124.6, 123.8, 118.1, 107.5, 55.3, 34.2, 24.8, 21.1, 20.3. IR (thin film) (cm^{-1}) ν: 3283, 1532, 1349, 1165. MS *m*/*z* (relative intensity): 389 (10), 388 (45), 202 (100), 172 (32), 122 (16), 76 (9). HR-MS (EI 70 eV) calcd. for $C_{19}H_{20}N_2O_5S$: 388.1093; found: 388.1091.

Acknowledgement

We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC), The Ontario Ministry of Science and Technology, and MedMira Laboratories for funding. S.C.B. is an NSERC PGSB scholar.

References

1. For an excellent review with many leading references see: K.C. Nicolaou, S.A. Snyder, T. Montagnon, and G. Vassilikogiannakis. Angew. Chem. Int. Ed. **41**, 1668 (2002).
2. M.A. Kerr. Synlett, 1165 (1995).
3. I.G.C.Coutts, N.J. Culbert, M. Edwards, J.A. Hadfield, D.R. Musto, V.H. Pavlidis, and D.J. Richards. J. Chem. Soc. Perkin Trans. 1, **9**, 1829 (1985).
4. (*a*) J.S. Swenton, B.R. Bonke, C.-P. Chen, and C.-T. Chou. J. Org. Chem. **54**, 51 (1989); (*b*) J.S. Swenton, C. Shih, C.-P. Chen, and C.-T. Chou. J. Org. Chem. **55**, 2019 (1990); (*c*) J.S. Swenton, B.R. Bonke, W.M. Clarke, C.-P. Chen, and K.V. Martin. J. Org. Chem. **55**, 2027 (1990).
5. S.C. Banfield and M.A. Kerr. Synlett, 436 (2001).
6. S.C. Banfield, D.B. England, and M.A. Kerr. Org. Lett **3**, 3323 (2001).
7. A. Pelter and S. Elgendy. Tetrahedron Lett. 677 (1988).
8. (*a*) F.-G. Klarner, M.K. Diedrich, and A.E. Wigger. *In* Chemistry under extreme or non-classical conditions. *Edited by* R. van Eldik and C.D. Hubbard. Wiley, New York. 1997. Chap 3; (*b*) J. Jurczak and D.T. Gryko. *In* Chemistry under extreme or non-classical conditions. *Edited by* R. van Eldik and C.D. Hubbard. Wiley, New York. 1997. Chap 4; (*c*) N.S. Isaacs. *In* High-pressure techniques in chemistry and physics. *Edited by* W.B. Holzapfel and N.S. Isaacs. Oxford, New York. 1997. Chap 7.
9. R.E. Heckert and H.R. Snyder. J. Am. Chem. Soc. **74**, 2006 (1952).
10. D.D. Perrin and W.L.F. Armarego. *In* Purification of laboratory chemicals. 3rd ed. Pergamon, New York. 1988.