Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 4279–4296

TETRAHEDRON: *ASYMMETRY*

Regio- and stereoselectivity in Diels–Alder reactions of 1,2-disubstituted dienes with enantiopure (S*S*)-(*p*-tolylsulfinyl)-1,4-benzoquinones

M. Carmen Carreño,* José L. García Ruano,* Cynthia Z. Remor† and Antonio Urbano

Departamento de Química Orgánica (C-I), Universidad Autónoma, Cantoblanco, 28049 Madrid, Spain

Received 26 July 2000; accepted 13 September 2000

Abstract

Reactions of 1,2-disubstituted dienes **1**–**3** with enantiopure sulfinylquinones **4**–**6** occur with similar π-facial diastereoselectivities but reversed regiochemistry under thermal conditions and in the presence of $ZnBr_2$. After spontaneous elimination of the sulfoxide, optically active polycyclic dihydroquinones are formed with ees ranging from 36 to >97%. The regiochemistry of the process is controlled by the alkyl substituent at C-1 in thermal reactions, whereas in the presence of $ZnBr_2$ the oxygenated function at C-2 becomes the main controller.

1. Introduction

The successful application of Diels–Alder reactions in synthesis stems from the possibility of controlling both the regio- and stereochemistry of the cycloaddition.[1] All these selective features have been exploited in the asymmetric version of the process.[2] The regiochemical course can be predicted taking into account the substitution on the dienophile and the diene partners. In the latter, the relative position of the substituent allows the major formation of *ortho* adducts, when it is situated at C-1, and *para* adducts, when this is at C-2, to be predicted. Such regioselectivity can be improved in the presence of Lewis acids.[3] When the diene bears two or more substituents, the regiochemistry of the process is generally controlled by the C-1 substituent, but, when a Lewis acid is added to the reaction medium, the regioselectivity can be inverted being strongly dependent on the reaction conditions as well as the Lewis acid.[4]

* Corresponding authors. E-mail: carmen.carrenno@uam.es; joseluis.garcia.ruano@uam.es

† On leave from Instituto de Química da Universidade Federal do Río Grande do Sul, Porto Alegre, Brazil.

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00365-7

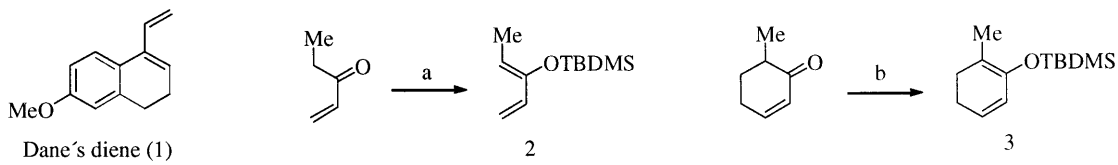
In the course of our work related to the asymmetric Diels–Alder reactions of (S*S*)-(*p*-tolylsulfinyl)quinones,[5] we have observed remarkable π-facial diastereoselectivities with a wide range of cyclic,[6] semicyclic[7] and acyclic[6a,b,8] dienes. We have also pointed out a different π-facial diastereoselection in reactions of cyclic or acyclic dienes in the presence of Lewis acids or under thermal conditions. The regiochemical outcome of these cycloadditions had been studied only with 1-substituted cyclic and acyclic dienes,[6a,b,9] but the behavior of more substituted dienes remained unknown. In particular, 1,2-disubstituted derivatives are of great interest since they open an easy access to highly substituted polycyclic compounds.[10–12] Among them, the well known 6-methoxy-1-vinyl-3,4-dihydronaphthalene (Dane's diene) **1**,[13] with activating substituents at C-1 and C-2, is one of the most frequently used in the construction of steroidal systems.[11]

In a preliminary communication[14] we have shown that the regiochemical course of Diels–Alder reactions of Dane's diene **1** with sulfinylquinones could be controlled by changing the reaction conditions (thermal or Lewis acid catalyst). We now report these results in full as well as the study of the regiochemistry of asymmetric Diels–Alder reactions between 1,2-disubstituted acyclic and cyclic dienes **2** and **3** and differently substituted enantiopure (*p*-tolylsulfinyl)-1,4-benzoquinones (+)-**4**, (+)-**5** and (+)-**6**. With such chiral dienophiles the regiochemical problem is superimposed on the stereochemical one. We disclose here that the regioselectivity is influenced by a remote substituent at C-5 of the 2-(*p*-tolylsulfinyl)-1,4-benzoquinone and show that the regiochemical inversion achieved in the presence of Lewis acids allows easy access to enantiomerically enriched regioisomeric polycyclic dihydroquinones.

2. Results

2.1. Synthesis of dienes

Dane's diene **1** was prepared according to a previously reported procedure.[15] The synthesis of 3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene **2** was planned through the transformation of commercially available ethyl vinyl ketone into the corresponding silylenol ether. After several trials using conventional procedures,[16] compound **2** could be obtained, as outlined in Scheme 1, following the methodology described by Evans for a similar derivative,[17] based on the treatment of the ketone precursor with solid KHMDS and further trapping of the formed enolate with *tert*-butyldimethylsilyl triflate. In the case of 1-methyl-2-(*tert*-butyldimethylsilyloxy)-1,3-cyclohexadiene **3** the synthesis was easily achieved from reaction of the known 6-methyl-2-cyclohexen-1-one[18] with lithium diisopropyl amine (LDA) and TBDMSOTf (Scheme 1).

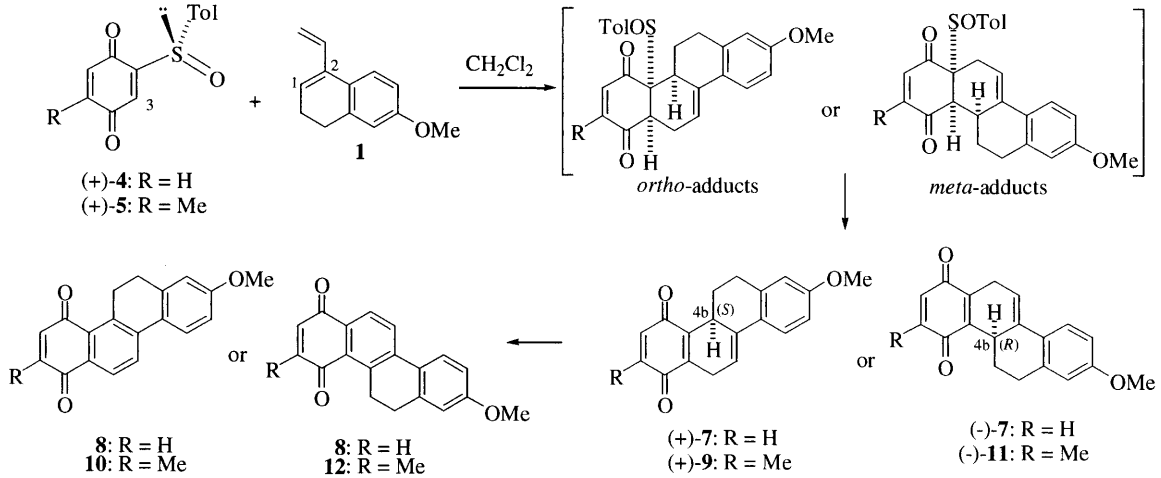


Scheme 1. (a) TBDMSOTf, KHMDS, THF, −78°C to rt, 1 h, 37%. (b) LDA, TBDMSOTf, THF, −20°C to rt, 2 h, 74%

2.2. Diels–Alder reactions

With the desired dienes in hand, we began the study of their Diels–Alder reactions with enantiopure sulfinylquinones **4**, **5** and **6** under thermal conditions and in the presence of $ZnBr_2$. In all cases the initial cycloaddition was followed by the pyrolytic elimination of the sulfoxide, which occurs even at −78°C, to recover the quinone structure in the final polycyclic product. The enantiomeric excesses of all optically active compounds obtained in these cycloadditions were measured by ^1H NMR using chiral lanthanide shift reagents, which required the preparation of each racemic derivative from the corresponding racemic sulfinylquinone.

Initially, we carried out the cycloadditions between Dane's diene **1** and enantiopure (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**4**.[19] The results obtained are depicted in Scheme 2 and Table 1. Working with 1 mol of **1** in CH_2Cl_2 at −78°C (entry 1), we observed the formation of optically active 8-methoxy-4b,5,6,12-tetrahydro-1,4-chrysenequinone (+)-**7**, resulting from the attack of the diene on the C_2–C_3 substituted double bond of **4** and elimination of the sulfoxide in the initially formed cycloadduct. Nevertheless, derivative (+)-**7** was not stable enough and evolved during the isolation process into a mixture of (+)-**7** and 8-methoxy-5,6-dihydro-1,4-chrysenequinone **8**, which could be separated after flash chromatography in 24 and 23% yield,



Scheme 2.

Table 1
Diels–Alder reactions of Dane's diene **1** and enantiopure sulfinylquinones (+)-**4** and (+)-**5**

Entry	Quinone	Lewis acid (equiv.)	*T* (°C)	*t* (h)	Products (% isolated yield)	Products (% ee)
1	(+)-**4**	–	−78	24	(+)-**7** (23)	(+)-**7** (80)
2	(+)-**4**	$ZnBr_2$ (2)	−20	0.25	(−)-**7** (20)	(−)-**7** (36)
3	(+)-**5**	–	−20	4	(+)-**9** (43)	(+)-**9** (80)
4	(+)-**5**	$ZnBr_2$ (2)	−20	2	(−)-**11** (38)	(−)-**11** (>97)
5	(+)-**5**	$BF_3{\cdot}OEt_2$ (5)	−20	0.25	(+)-**9**+(−)-**11**[a]	[b]

[a] Obtained as a 25:75 mixture.
[b] Not determined.

respectively. When reactions were conducted at higher temperatures or with an excess of the diene, variable mixtures of (+)-**7**, **8** and bisadducts resulting from a double cycloaddition process were obtained. Tetracyclic quinone (+)-**7** showed a specific rotation of $[\alpha]_D^{20}=+94$ (*c* 0.12, $CHCl_3$) and 80% enantiomeric purity [Yb(hfc)$_3$]. The absolute configuration at C-4b, the only stereogenic center of (+)-**7**, was assigned as (*S*) taking into account the behavior of sulfinylquinones as dienophiles in cycloadditions with acyclic dienes under thermal conditions[6a] which reacted from the less hindered face of the most reactive *s-cis* conformation shown in Scheme 1.

The same reaction in the presence of $ZnBr_2$ (Table 1, entry 2) afforded the corresponding enantiomer (–)-**7**. After flash chromatography we isolated a 20% yield of (–)-**7** and a 25% yield of aromatic compound **8**. Derivative **7** showed an optical rotation of $[\alpha]_D^{20}=-46$ (*c* 0.12, $CHCl_3$) indicating 36% enantiomeric purity. Comparison with the rotary power of (+)-**7** allowed us to assign the (*R*) absolute configuration to the major enantiomer of (–)-**7**. Since no substituent remained in the quinone moiety, the formation of (–)-**7** could be a consequence of a change in the regiochemistry or in the π-facial diastereoselectivity of the process. According to literature data related to the use of Dane's diene,[11] the former reason seemed more suitable, but our earlier observation of a reversed π-facial selectivity of the Diels–Alder reactions with cyclic dienes in the presence of $ZnBr_2$ could point to the latter.[6a,b,9]

In order to ascertain the origin of the change in the specific rotation of **7** and determine the exact regiochemistry of the cycloaddition process, we thought of using enantiopure (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5**[20] as dienophile (Scheme 2 and Table 1). Under thermal conditions (entry 3), the Diels–Alder reaction of Dane's diene **1** and (+)-**5** afforded only one regioisomer, 8-methoxy-2-methyl-4b,5,6,12-tetrahydro-1,4-chrysenequinone (+)-**9**, resulting from the spontaneous elimination of the sulfinyl group in the initially formed *ortho*-cycloadduct. After flash chromatography, compound (+)-**9** and aromatic derivative 8-methoxy-2-methyl-5,6-dihydro-1,4-chrysenequinone **10** were isolated in 43 and 24% yield, respectively. This result indicated that the alkyl substituent at C-1 of the diene directed the regiochemistry of the process under thermal conditions. Quinone (+)-**9** showed a specific rotation of $[\alpha]_D^{20}=+134$ (*c* 0.13, $CHCl_3$) with 80% enantiomeric purity [Yb(hfc)$_3$] and the (*S*) absolute configuration at C-4b.

When the cycloaddition of diene **1** and sulfinylquinone (+)-**5** was carried out in the presence of $ZnBr_2$ (Table 1, entry 4), we obtained 8-methoxy-3-methyl-4b,5,6,12-tetrahydro-1,4-chrysenequinone (–)-**11**, resulting from the pyrolytic elimination of the sulfoxide in the exclusively *meta*-adduct[21] initially formed, whose structure showed the opposite regiochemistry to that of (+)-**9**. After flash chromatography, compound (–)-**11** and aromatic derivative 8-methoxy-3-methyl-5,6-dihydro-1,4-chrysenequinone **12** were isolated in 38 and 22% yield, respectively. Quinone (–)-**11** showed a specific rotation of $[\alpha]_D^{20}=-185$ (*c* 0.21, $CHCl_3$) with >97% enantiomeric purity [Yb(hfc)$_3$] and the (*R*) absolute configuration at C-4b.

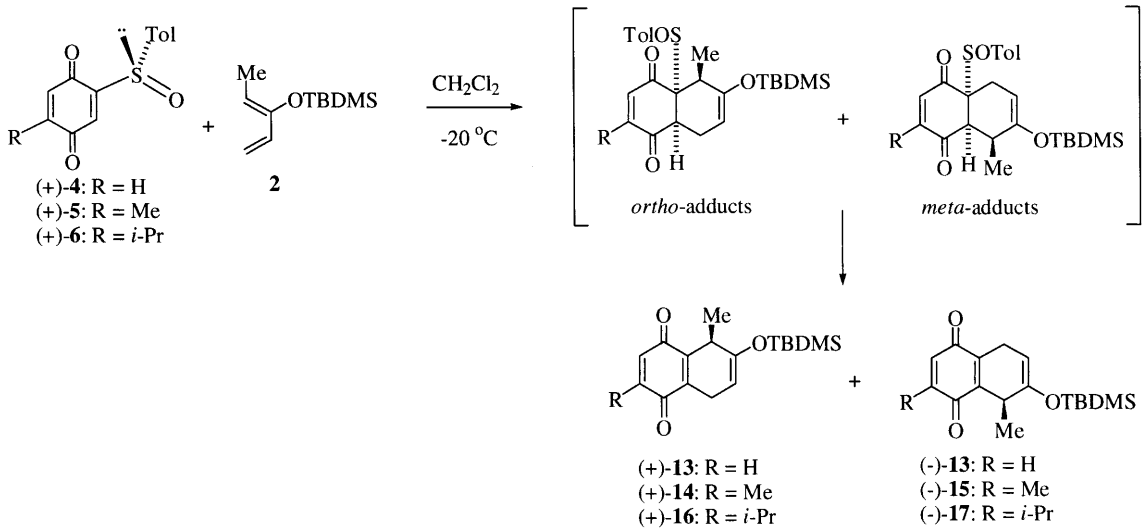
The regiochemical result achieved in this case indicated that the *p*-methoxyphenyl substituent at C-2 of Dane's diene was directing the regiochemical course of the Diels–Alder reaction in the presence of the Lewis acid and confirmed that the change observed in the specific rotation for derivative **7** working under thermal or $ZnBr_2$ catalyzed conditions was due to a change in the regiochemistry and not in the π-facial diastereoselectivity of the process.

The inversion of regiochemistry in cycloadditions with Dane's diene under Lewis acid conditions was confirmed when the reaction of **1** and (+)-**5** was performed in the presence of $BF_3{\cdot}OEt_2$ (Table 1, entry 5). In this case, a 25:75 mixture of regioisomers (+)-**9** and (–)-**11** was obtained, (–)-**11** being predominant. When this reaction was carried out with minor amounts of

$BF_3{\cdot}OEt_2$ and/or lower temperatures, the ratio (+)-**9**:(−)-**11** changed in favor of **9**, showing a decreasing association between the Lewis acid and the basic center of diene **1**. Different regiochemical outcome has been already observed for Diels–Alder reactions of substituted benzoquinones with 1,2-disubstituted dienes in the presence of different Lewis acids and/or solvents.[4h]

The structural assignment of derivatives **7** and **8** was based on a detailed analysis of their spectroscopic parameters (see Section 5). Nevertheless, these spectroscopic data were not enough for the structural assignment of regioisomeric **9** and **11** as well as for that of aromatic derivatives **10** and **12**. Finally, the structural assignment of compound **9** was established from ^{13}C–^1H NMR bidimensional correlations through one bond (HMQC) or multiple bonds (HMBC).[22] Moreover, the X-ray ORTEP of aromatic derivative **10** showed the relative disposition of methyl and methoxy groups shown in Scheme 1 for this compound as well as for its precursor **9** and confirmed the *ortho* regiochemistry of the initial cycloaddition.

Once the cycloadditions with Dane's diene **1** were studied, we undertook the Diels–Alder reactions between acyclic diene **2** and enantiopure sulfinylquinones (+)-**4**, (+)-**5** and (+)-**6**[20] under thermal and $ZnBr_2$ catalyzed conditions. The results obtained are depicted in Scheme 3 and Table 2. In all cases cycloadditions occurred through the sulfinyl substituted C_2–C_3 double bond of sulfinylquinones to afford the corresponding 5,8-dihydronaphthoquinones, which partially aromatized to the corresponding naphthoquinones during the isolation process. When a regioisomeric mixture of substituted 5,8-dihydronaphthoquinones was formed, the regioisomer ratios were determined directly from the crude reaction mixtures by integration of well separated signals in the ^1H NMR spectra.



Scheme 3.

The reaction of diene **2** and sulfinylquinone (+)-**4** under thermal conditions (Table 2, entry 1) afforded racemic 6-(*tert*-butyldimethylsilyloxy)-5-methyl-5,8-dihydro-1,4-naphthoquinone **13**. Nevertheless, when the cycloaddition was performed in the presence of $ZnBr_2$ (entry 2), we isolated derivative (−)-**13** in optically active form, $[\alpha]_D^{20} = -49$ (*c* 0.14, $CHCl_3$), with 70% enantiomeric excess [$Pr(hfc)_3$].

Table 2
Diels–Alder reactions of acyclic diene **2** and enantiopure sulfinylquinones (+)-**4**, (+)-**5** and (+)-**6** at −20°C

Entry	Quinone	Lewis acid (equiv.)	*t* (h)	Products (ratio)	Products (% isolated yield)	Products (ee)
1	(+)-**4**	–	48	(±)-**13**	**13** (32)	**13** (0)
2	(+)-**4**	$ZnBr_2$ (2)	0.25	(−)-**13**	**13** (36)	**13** (70)
3	(+)-**5**	–	48	(+)-**14** (50)+(−)-**15** (50)	**14** (25) **15** (22)	**14** (78) **15** (72)
4	(+)-**5**	$ZnBr_2$ (2)	0.1	(+)-**14** (0)+(−)-**15** (100)	**15** (42)	**15** (72)
5	(+)-**6**	–	56	(+)-**16** (80)+(−)-**17** (20)	**16** (40) **17** (10)	**16** (>97) **17** (74)
6	(+)-**6**	$ZnBr_2$ (2)	1	(+)-**16** (0)+(−)-**17** (100)	**17** (62)	**17** (74)

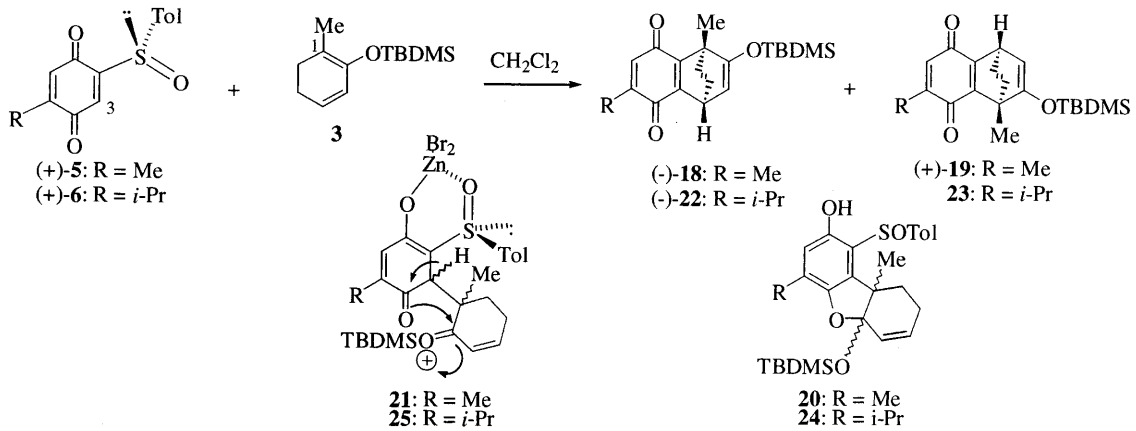
The regiochemistry of the process could be established after the cycloadditions of **2** with substituted sulfinylquinones (+)-**5** and (+)-**6** (Scheme 3 and Table 2). Thus, the reaction between **2** and (+)-**5** under thermal conditions (Table 2, entry 3) afforded a 50:50 mixture of regioisomeric 6-(*tert*-butyldimethylsilyloxy)-2,5-dimethyl-5,8-dihydro-1,4-naphthoquinone **14** and 7-(*tert*-butyldimethylsilyloxy)-2,8-dimethyl-5,8-dihydro-1,4-naphthoquinone **15** in optically active form, which could be separated by flash chromatography. This result indicated that the regiodirecting power of both the alkyl substituent at C-1 and the silyloxy group at C-2 was very similar under these conditions and contrasted with the result obtained in the reaction of the same quinone (+)-**5** with Dane's diene (Table 1, entry 3) where only one regioisomer was formed under thermal conditions. Compound (+)-**14** showed a specific rotation of $[\alpha]_D^{20}=+28$ (*c* 0.84, $CHCl_3$) with 78% enantiomeric excess [Pr(hfc)$_3$], whereas that of (−)-**15** was $[\alpha]_D^{20}=-29$ (*c* 0.33, $CHCl_3$) and 72% enantiomeric excess [Pr(hfc)$_3$]. In the presence of $ZnBr_2$ (Table 2, entry 4), the reaction of **2** and (+)-**5** afforded compound (−)-**15** {$[\alpha]_D^{20}=-29$ (*c* 0.37, $CHCl_3$), 72% ee} as the only regioisomer, proceeding from the *meta*-adduct initially formed. In this case, the regiochemistry of the process was totally controlled by the oxygenated substituent at C-2.

The structural assignment of regioisomers **14** and **15** was very difficult due to the very similar spectroscopic parameters of both compounds (see Section 5). Nevertheless, the correct structure of derivative **15** was confirmed from HMBC experiments[22] which showed the regiochemistry indicated in Scheme 3. Taking into account this consideration, we assigned the 2,5,6-trisubstituted-5,8-dihydro-1,4-naphthoquinone structure to major derivatives obtained under thermal conditions and the 2,7,8-trisubstitution for regioisomers formed in the presence of $ZnBr_2$.

When cycloaddition of acyclic diene **2** was performed with enantiopure (S*S*)-2-isopropyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**6**[20] under thermal conditions (Scheme 3, Table 2, entry 5), an 80:20 mixture of regioisomeric 6-(*tert*-butyldimethylsilyloxy)-2-isopropyl-5-methyl-5,8-dihydro-1,4-naphthoquinone (+)-**16** and 7-(*tert*-butyldimethylsilyloxy)-2-isopropyl-8-methyl-5,8-dihydro-1,4-naphthoquinone (−)-**17** was formed. Both dihydronaphthoquinones could be separated by flash chromatography. Compound (+)-**16** showed a specific rotation of $[\alpha]_D^{20}=+49$ (*c* 1.2, $CHCl_3$) with an enantiomeric excess >97% [Pr(hfc)$_3$], whereas that of (−)-**17** was $[\alpha]_D^{20}=-47$ (*c* 0.8, $CHCl_3$) with 74% enantiomeric excess [Pr(hfc)$_3$]. The regioselectivity which resulted in this reaction contrasted with that obtained in the cycloaddition between the same diene **2** and

sulfinylquinone (+)-**5** under similar thermal conditions (50:50 mixture of regioisomers was formed) and suggested that the presence of a remote methyl versus an isopropyl group at C-5 in quinones **5** and **6** was influencing the regiochemical course of the reaction. In the presence of $ZnBr_2$ (Table 2, entry 6), the reaction of **2** and (+)-**6** gave rise to compound (−)-**17** {$[\alpha]_D^{20} = -46$ (*c* 0.8, $CHCl_3$), 74% ee} in a regioselective way showing again that, under these conditions, the oxygenated substituent at C-2 is governing the regiochemistry of the reaction.

Finally, we carried out the Diels–Alder reactions between cyclic diene **3** and substituted sulfinylquinones (+)-**5** and (+)-**6** (Scheme 4, Table 3). As can be seen, in all cases reactions took place chemoselectively on the sulfinyl substituted double bond of quinones. Thermal cycloadditions did not occurr at −20°C being necessary to heat to room temperature as a consequence of the lower reactivity of cyclic diene **3** with respect to that of dienes **1** and **2**.



Scheme 4.

Table 3
Diels–Alder reactions of cyclic diene **3** and enantiopure sulfinylquinones (+)-**5** and (+)-**6**

Entry	Quinone	Lewis acid (equiv.)	*T* (°C)	*t* (h)	Products (ratio)	Products (% isolated yield)	Products (ee)
1	(+)-**5**	–	rt	48	(−)-**18** (75) **19** (25)	**18** (37)	**18** (>97) **19** (78)[a]
2	(+)-**5**	$ZnBr_2$ (2)	−40	5	**18** (0) (+)-**19** (10) **20**[b] (90)	**19** (7) **20** (56)	**19** (78)
3	(+)-**6**	–	rt	18	(−)-**22** (93) **23** (7)	**22** (30)	**22** (84) **23** (82)[c]
4	(+)-**6**	$ZnBr_2$ (2)	−40	6	**22** (0) **23** (0) **24**[b] (100)	**24** (48)	

[a] Measured from the mixture of **18** and **19**.
[b] Obtained as a 60:40 mixture of diastereoisomers.
[c] Measured from the mixture of **22** and **23**.

So, the cycloaddition between quinone (+)-**5** and diene **3** (entry 1) afforded a 75:25 mixture of regioisomeric 6-(*tert*-butyldimethylsilyloxy)-5,8-ethane-2,5-dimethyl-5,8-dihydro-1,4-naphthoquinone **18** and 7-(*tert*-butyldimethylsilyloxy)-5,8-ethane-2,8-dimethyl-5,8-dihydro-1,4-naphthoquinone **19**, from which only derivative (−)-**18** could be isolated pure by flash chromatography.

Compound **18** showed a specific rotation of $[\alpha]_D^{20} = -67$ (*c* 0.4, $CHCl_3$) with an enantiomeric excess >97% [Pr(hfc)$_3$], whereas the enantiomeric excess of **19** was 78% [Pr(hfc)$_3$] from the mixture of **18** and **19**. The higher regioselectivity achieved in this reaction contrasted with that resulting in the cycloaddition of acyclic diene **2** with the same sulfinylquinone (+)-**5** where no regioselectivity was observed. This different behavior was striking since the substitution at C-1 and C-2 of dienes **2** and **3** was very similar.

When the reaction was conducted in the presence of $ZnBr_2$ (entry 2), we observed the formation of a 10:90 mixture of derivative **19**, proceeding from the Diels–Alder reaction, and 5a-(*tert*-butyldimethylsilyloxy)-4,9a-dimethyl-1-(*p*-tolylsulfinyl)-5a,8,9,9a-tetrahydrodibenzofuran-2-ol **20**, isolated and characterized as a 60:40 mixture of diastereoisomers. The formation of these type of derivatives had been already pointed out by several authors in similar reactions of enol ethers with activated quinones[23] and could be explained from the nucleophilic attack of the electron rich C-1 position of cyclic diene **3** to the more electron deficient C-3 position of sulfinylquinone **5** to afford an intermediate such as **21** which, after aromatization and intramolecular nucleophilic attack of the quinonic oxygen to the charge deficient carbon, evolved to the corresponding diastereoisomers **20** (Scheme 4). Although the ratio of compound **19** resulting from the Diels–Alder reaction was very low (10%), its formation confirmed that in the presence of the Lewis acid the regioselectivity is directed by the oxygenated substituent at C-2 of diene **3** which gave rise to the formation of the *meta*-adduct. Derivative **19** showed a specific rotation of $[\alpha]_D^{20} = +23$ (*c* 0.47, $CHCl_3$) and 78% ee [Pr(hfc)$_3$].

When cycloaddition was performed between cyclic diene **3** and enantiopure sulfinylquinone (+)-**6** under thermal conditions (Scheme 4, Table 3, entry 3), a 93:7 mixture of regioisomeric 6-(*tert*-butyldimethylsilyloxy)-5,8-ethane-2-isopropyl-5-methyl-5,8-dihydro-1,4-naphthoquinone **22** and 7-(*tert*-butyldimethylsilyloxy)-5,8-ethane-2-isopropyl-8-methyl-5,8-dihydro-1,4-naphthoquinone **23** was formed. From this mixture, only compound (–)-**22** could be isolated pure by flash chromatography. This regiochemical result indicated that the alkyl substituent at C-1 of diene **3** was almost exclusively directing the regiochemistry of the process under these conditions. Derivative **22** showed a specific rotation of $[\alpha]_D^{20} = -51$ (*c* 0.65, $CHCl_3$) with 84% enantiomeric excess [Pr(hfc)$_3$], whereas the enantiomeric excess of **23** was 82% [Pr(hfc)$_3$] from the mixture of **22** and **23**.

When the reaction of **3** and (+)-**6** was conducted in the presence of $ZnBr_2$ (entry 4), no product deriving from the cycloaddition process was detected. We only isolated 5a-(*tert*-butyldimethylsilyloxy)-4-isopropyl-9a-methyl-1-(*p*-tolylsulfinyl)-5a,8,9,9a-tetrahydrodibenzofuran-2-ol **24** as a 60:40 mixture of diastereoisomers formed through the cationic intermediate **25** in a similar way to that indicated for compound **20** (Scheme 4).

3. Discussion

To rationalize the results achieved in these reactions we must differentiate the regioselectivity and the π-facial diastereoselectivity. The observed regioselectivity was in turn different when reactions were carried out under thermal or Lewis acid catalyzed conditions.

Reactions of methyl substituted quinone **5** under thermal conditions led to the major formation of *ortho*-adduct from cyclic diene **3** (Table 3, entry 1), which became exclusive from

semicyclic Dane's diene (Table 1, entry 3). No regioselectivity was observed when the reacting diene was the acyclic butadiene derivative **2** (Table 2, entry 1). Considering the role played by the coefficients of the atomic orbitals of the HOMO of C-1 and C-2 substituted dienes[3] in the control of the regioselectivity of Diels–Alder reactions, the formation of a mixture of *ortho*-(C-1 control) and *meta*-(C-2 control) adducts should be expected for dienes **1**, **2**, and **3**, but this was only the case for **2**. If we consider the *endo* transition states giving rise to both regioisomers (TSI and TSII in Fig. 1) we can observe a R (CH_3)/R′ destabilizing interaction in that leading to the *meta*-adduct, *meta*-TSII, which does not exist in the *ortho* transition state *ortho*-TSI. Such steric interaction must be stronger for the transition state resulting from Dane's diene **1** where R′ is a bulky aromatic group and could explain the exclusive evolution through the *ortho* transition state. When dienes **2** and **3** are reacting, such interaction is similar since in both cases R′ is a OTBDMS group. The major formation of the *ortho*-adduct from cyclic diene **3** must be a consequence of a distorted geometry of the *endo–meta* transition state (*meta*-TSIII in Fig. 1) due to the destabilizing interaction existent between the methylene bridges of the diene and the sulfoxide group of the quinone which forces an out-of-plane disposition when the dienophile is approaching. As a consequence, the R′ substituent must be shifted to the bottom face (see Fig. 1) determining an increased R/R′ (OTBDMS) interaction. The higher energy content of this transition state would explain the preferred evolution through the more stable *ortho* transition state leading to the major formation of **18**.

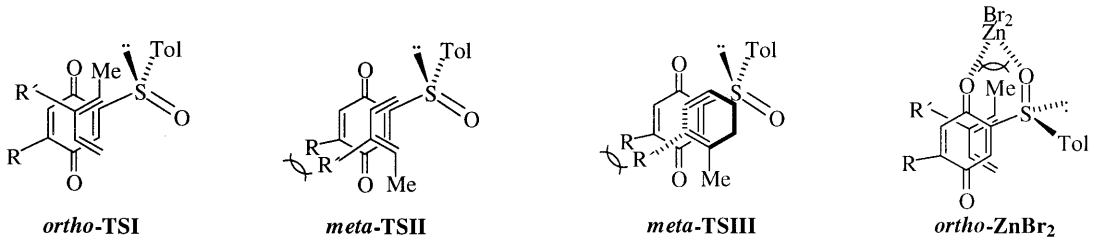


Figure 1.

The results obtained in the reactions of dienes **2** and **3** with 5-isopropyl-(2-*p*-tolylsulfinyl)-1,4-benzoquinone **6** reinforce the above explanation. The R (*i*-Pr)/R′ interaction existing in the *meta*-TSII transition state (Fig. 1) is now stronger and, as a consequence, the evolution through the most stable *ortho* transition state is preferred for **2** (80:20 ratio of **16** and **17**, Table 2, entry 5) and **3** (93:7 ratio of **22** and **23**, Table 3, entry 3). In the latter, the distorted geometry of the transition state resulting from the cyclic diene approach must also contribute to the preferred formation of **22**. The higher preference for *ortho* regioisomers from 5-isopropyl derivative with respect to the similar reactions with 5-methyl-2-(*p*-tolylsulfinyl)-1,4-benzoquinone must be due to the higher destabilization of the *meta* transition state when R = *i*-Pr with respect to R = Me.

The regiochemical course of reactions with unsubstituted 2-(*p*-tolylsulfinyl)-1,4-benzoquinone **4** can be deduced from the enantiomeric excess of the resulting compounds (+)-**7** (80% ee, Table 1, entry 1) and **13** (racemic, Table 2, entry 1). The enantiomeric excess of (+)-**7** is identical to that observed for (+)-**9** suggesting that both quinones **4** and **5** evolve with similar π-facial diastereoselectivities under thermal conditions. Therefore, the regioselectivity must be almost

identical for both quinones. Racemic **13** must result from the formation of an equimolecular mixture of (+)-**13** and (–)-**13** resulting in a reaction with null regioselectivity in the same way observed in the reaction of (+)-**5** with diene **2**. This result indicates that under thermal conditions the regioselectivity of the process is scarcely modified when the R substituent of the quinone is H or Me.

When $ZnBr_2$ was present in the reaction medium, the exclusive formation of *meta*-adducts both from methyl substituted quinone **5** (Table 1, entry 4; Table 2, entry 4 and Table 3, entry 2) and the isopropyl substituted dienophile **6** (Table 2, entry 6) was observed. These results could be explained invoking the Frontier Orbital theory taking into account that the coordination of the Lewis acid to the OMe group of Dane's diene **1** or the OTBDMS substituent of dienes **2** and **3** must induce significant changes in the coefficients of their HOMO bringing about the major C-2 regiocontrol. The efficiency of $ZnBr_2$ in inverting the regiochemistry with respect to thermal reactions is higher than that of $BF_3{\cdot}OEt_2$ (see Table 1, entries 4 and 5). Since the effect of both Lewis acids on the orbital coefficients must be similar, other effects must be invoked to account for such differences. Considering the ability of the $ZnBr_2$ to form doubly associated species with sulfinyl benzoquinones,[9] the *ortho* cycloaddition through the chelated species *ortho*-$ZnBr_2$ represented in Fig. 1 must be strongly disfavored due to the steric congestion existing between the sulfinyl and carbonyl oxygens and the substituent at C-1 of the diene, leading to the exclusive *meta* evolution of the process

According to the enantiomeric excesses of compounds obtained from quinones **5** and **6**, the π-facial diastereoselectivities of these reactions range from 72 to >97% being slightly higher when the *ortho*-adducts are formed. The absolute configuration of the stereogenic centers indicated in Schemes 1–3 for products resulting from thermal reactions must be a consequence of the well-known[5,6] preferred evolution of sulfinylquinones through the *s-cis* conformation from the less hindered top face bearing the lone electron pair of the sulfoxide (Fig. 1). For reactions carried out in the presence of $ZnBr_2$, the absolute configuration of the stereogenic centers existing in the final products could not be unequivocally established, but the enantiomeric excesses determined ranged from 36 to 97%. While we do not have a convincing explanation for the moderate to excellent π-facial diastereoselectivity observed under $ZnBr_2$ catalyzed conditions, it is noteworthy that this Lewis acid was able to efficiently invert the regioselectivity of these processes due to the cooperation of orbital factors and steric interactions with the remote C-5 substituent of the sulfinyl benzoquinone.

4. Conclusion

The results presented show that the regioselectivity of Diels–Alder reactions of (*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinones **5** and **6** can be directed by the adequate choice of thermal or $ZnBr_2$ catalyzed conditions. Such possibility allows the stereoselective synthesis of two regioisomers of tetrahydrochrysenequinones **9** and **11** from Dane's diene as well as dihydronaphthoquinones **14**–**17** from 3-*tert*-butyldimethylsilyloxy-1,3-pentadiene. When 2-*tert*-butyldimethylsilyloxy-1-methyl-1,3-cyclohexadiene was used as the diene partner, the competitive formation of dibenzofuran derivatives **20** and **24** in the presence of $ZnBr_2$ prevented the efficient synthesis of regioisomeric 5,8-ethano-5,8-dihydro-1,4-naphthoquinones **19** and **23**.

5. Experimental

5.1. General methods

Melting points were obtained in open capillary tubes and are uncorrected. IR spectra were obtained as $CHCl_3$ solutions and are given in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively. Regioisomeric adducts ratios were established by integration of well-separated signals in the crude reaction mixtures and are listed in Tables 1–3. All reactions were monitored by thin layer chromatography that was performed on precoated sheets of silica gel 60, and flash column chromatography was performed with silica gel 60 (230–400 mesh) of Macherey–Nagel. Eluting solvents are indicated in the text. Apparatuses for inert atmosphere experiments were dried by flaming in a stream of dry argon. Dry THF was distilled from sodium/benzophenone ketyl. CH_2Cl_2 and $CHCl_3$ were dried over P_2O_5. For routine workup, hydrolysis was carried out with water, extractions with CH_2Cl_2, and solvent dryness with Na_2SO_4.

5.2. (*Z*)-3-(tert-*Butyldimethylsilyloxy*)-1,3-pentadiene **2**

To a solution of 1-penten-3-one (1.63 g, 20 mmol) and TBDMSOTf (5.5 ml, 24 mmol) in dry THF (150 ml) at −78°C under argon, a suspension of KHMDS (4.0 g, 20 mmol) in dry THF (60 ml) was slowly added and the reaction continued at −78°C for 30 min and at rt for 1 h. The mixture was hydrolyzed with $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with NaCl and dried with $MgSO_4$. The residue was purified by flash chromatography (eluent hexane) to obtain pure **2** as a colorless oil in 37% yield; ^1H NMR: δ 6.20 (dd, 1H, $J=17.1$ and 10.7 Hz), 5.32 (dd, 1H, $J=17.1$ and 10.8 Hz), 4.96 (dd, 1H, $J=10.7$ and 10.8 Hz), 4.90 (q, 1H, $J=7.0$ Hz), 1.69 (d, 3H, $J=7.0$ Hz), 1.02 (s, 9H), 0.12 (s, 6H); ^{13}C NMR: δ 149.4, 135.6, 111.6, 110.0, 26.0 (3C), 18.4, 11.8, −2.9, −3.6.

5.3. 2-(tert-*Butyldimethylsilyloxy*)-1-methyl-1,3-cyclohexadiene **3**

To a solution of diisopropylamine (492 mg, 4.86 mmol) in dry THF (16 ml) at −25°C under argon, *n*-BuLi 2.02 M (2.3 ml, 4.65 mmol) was added. After 30 min, 6-methyl-2-cyclohexenone[18] (466 mg, 4.23 mmol) was added and the reaction continued for 30 min at the same temperature. Then, TBDMSOTf (1.02 ml, 4.44 mmol) was added and after 1 h at rt the mixture was diluted with pentane and extracted with $NaHCO_3$. After workup, the residue was purified by flash chromatography over silica gel previously neutralized with a 10% solution of triethylamine in pentane and washed three times with pentane (eluent pentane) to obtain pure **3** as a colorless oil in 74% yield; ^1H NMR: δ 5.68 (broad s, 2H), 2.10 (broad s, 4H), 1.67 (broad s, 3H), 0.96 (s, 9H), 0.95 (s, 6H); ^{13}C NMR: δ 142.0, 126.4, 125.2, 112.4, 28.7, 23.0, 25.8 (3C), 18.1, 16.1, −4.2 (2C); EI-MS: m/z (%) 224 (M^+, 10), 183 (31), 109 (21), 75 (100), 73 (74); HRMS (EI) calcd for $C_{13}H_{24}OSi$: 224.15964; found: 224.15826.

5.4. General procedure for thermal Diels–Alder reactions. Method A

To a solution of the (*p*-tolylsulfinyl)-1,4-benzoquinone (0.4 mmol) in 5 ml of dry CH_2Cl_2 at the temperature indicated in each case (see Tables 1–3 for reaction conditions) under argon, the

corresponding diene (0.4 mmol) was added. After the time required and evaporation of the solvent, crude dihydroquinones were obtained and purified by flash chromatography.

5.5. General procedure for $ZnBr_2$ catalyzed Diels–Alder reactions. Method B

To a vigorously stirred suspension of dry $ZnBr_2$ (0.8 mmol) in dry CH_2Cl_2 under argon, the (*p*-tolylsulfinyl)-1,4-benzoquinone (0.4 mmol) in 5 ml of dry CH_2Cl_2 was added. After 1 h at rt, the mixture was cooled to −20°C and the corresponding diene (0.4 mmol) was added. After the time required in each case (see Tables 1–3 for reaction conditions) and workup, crude dihydroquinones were obtained and purified by flash chromatography.

5.6. (4*b*S)-8-Methoxy-4b,5,6,12-tetrahydro-1,4-chrysenequinone (+)-**7**

Compound (+)-**7** was obtained from (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone[19] (+)-**4** and Dane's diene[15] **1** (1 M in benzene) following method A at −78°C for 24 h (eluent hexane:EtOAc 90:10) as an orange solid in 23% yield; mp 158–159°C; $[\alpha]_D^{20}=+94$ (*c* 0.12, $CHCl_3$), ee = 80% [Yb(hfc)$_3$]; ^{1}H NMR: δ 7.38 (d, 1H, $J=8.5$ Hz), 6.76 (dd, 1H, $J=8.5$ Hz, and 2.9 Hz), 6.75 (s, 2H), 6.65 (d, 1H, $J=2.9$ Hz), 5.97–5.90 (m, 1H), 3.80 (s, 3H), 3.53–3.40 (m, 1H), 3.32–2.83 (m, 4H), 2.51–2.40 (m, 1H), 1.70–1.50 (m, 1H); ^{13}C NMR: δ 187.1, 187.0, 159.1, 150.0, 141.8, 137.4, 137.0, 135.9, 134.7, 128.7, 125.3, 113.2, 113.0, 112.6, 55.2, 35.0, 31.5, 30.3, 28.5; IR ν_{max}: 2980, 2880, 1645, 1595, 1125; EI-MS: *m*/*z* (%) 292 (M^+, 27), 290 (100), 277 (11), 261 (17), 247 (20), 219 (11), 189 (17), 165 (17), 147 (12), 94 (7); HRMS (EI) calcd for $C_{19}H_{16}O_3$: 292.10995; found: 292.11022.

5.7. (4*b*R)-8-Methoxy-4b,5,6,12-tetrahydro-1,4-chrysenequinone (−)-**7**

Compound (−)-**7** was obtained from (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**4** and Dane's diene **1** (1 M in benzene) following method B for 15 min (eluent hexane:EtOAc 90:10) as an orange solid in 20% yield; $[\alpha]_D^{20}=-42$ (*c* 0.12, $CHCl_3$), ee = 36% [Yb(hfc)$_3$].

5.8. 8-Methoxy-5,6-dihydro-1,4-chrysenequinone ***8***

Compound **8** was obtained from (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**4** and Dane's diene **1** (1 M in benzene) following method A at −78°C for 24 h or following method B for 15 min (eluent hexane:EtOAc 90:10) as an orange solid in 23 and 25% yield, respectively; mp 187–188°C; ^{1}H NMR: δ 8.09 and 8.00 (AB system, 2H, $J=8.2$ Hz), 7.69 (d, 1H, $J=8.6$ Hz), 6.91 (s, 2H), 6.85 (dd, 1H, $J=8.6$ and 2.8 Hz), 6.83 (d, 1H, $J=2.8$ Hz), 3.87 (s, 3H), 3.53 and 2.83 (2dd, 4H, $J=7.4$, 7.0 Hz); ^{13}C NMR: δ 187.7, 184.9, 160.5, 141.6, 140.6, 139.8, 139.3, 140.0, 135.9, 131.2, 127.8, 126.2, 125.8, 125.3, 113.2, 113.0, 55.3, 28.5, 25.3; IR ν_{max}: 3110, 2990, 2920, 1650, 1600, 1130; EI-MS: *m*/*z* (%) 290 (M^+, 100), 277 (9), 261 (17), 247 (10), 231 (9), 219 (11), 189 (17), 165 (17), 147 (6), 101 (6). Anal. calcd for $C_{19}H_{14}O_3$: C, 78.60; H, 4.86. Found: C, 78.78; H, 4.99.

5.9. Compound (4*b*S)-8-Methoxy-2-methyl-4b,5,6,12-tetrahydro-1,4-chrysenequinone (+)-***9***

Compound (+)-**9** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone[20] (+)-**5** and Dane's diene **1** (1 M in benzene) following method A at −20°C for 4 h (eluent hexane:EtOAc 95:5) as a red solid in 43% yield; mp 128–129°C; $[\alpha]_D^{20}=+134$ (*c* 0.13, $CHCl_3$),

ee = 80% [Yb(hfc)$_3$]; ^{1}H NMR: δ 7.38 (d, 1H, J = 8.5 Hz), 6.74 (dd, 1H, J = 8.5 and 2.4 Hz), 6.64 (d, 1H, J = 2.4 Hz), 6.59 (q, 1H, J = 1.6 Hz), 5.98–5.92 (m, 1H), 3.80 (s, 3H), 3.52–3.35 (m, 1H), 3.32–2.82 (m, 4H), 2.53–2.41 (m, 1H), 2.06 (d, 3H, J = 1.6 Hz), 1.68–1.51 (m, 1H); ^{13}C NMR: δ 187.6, 187.1, 159.1, 145.1, 141.6, 139.1, 137.4, 134.7, 132.8, 125.3, 113.3, 113.2, 112.5, 55.2, 34.9, 31.5, 30.3, 25.4, 15.6; IR ν_{max}: 2990, 1640, 1600, 1130. Anal. calcd for $C_{20}H_{18}O_3$: C, 78.40; H, 5.93. Found: C, 78.51; H, 6.02.

5.10. 8-Methoxy-2-methyl-5,6-dihydro-1,4-chrysenequinone **10**

Compound **10** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5** and Dane's diene **1** (1 M in benzene) following method A at −20°C for 4 h (eluent hexane:EtOAc 95:5) as a red solid in 24% yield; mp 138–139°C (hexane); ^{1}H NMR: δ 8.08–7.95 (AB system, 2H, J = 8.2 Hz), 7.67 (d, 1H, J = 8.6 Hz), 6.88 (dd, 1H, J = 2.6 and 8.5 Hz), 6.81 (d, 1H, J = 2.6 Hz), 6.76 (q, 1H, J = 1.4 Hz), 3.86 (s, 3H), 3.52 and 2.81 (2m, 4H), 2.14 (d, 3H, J = 1.4 Hz); ^{13}C NMR: δ 187.8, 185.5, 160.4, 146.3, 141.3, 139.8, 137.5, 137.7, 131.5, 127.5, 126.2, 126.0, 126.0, 113.1, 113.0, 112.9, 55.4, 28.6, 25.3, 15.9; IR ν_{max}: 3000, 2950, 1640, 1600, 1130. Anal. calcd for $C_{20}H_{16}O_3$: C, 78.92; H, 5.30. Found: C, 79.08; H, 5.21.

5.11. (4*b*R)-8-Methoxy-3-methyl-4b,5,6,12-tetrahydro-1,4-chrysenequinone (−)-**11**

Compound (−)-**11** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5** and Dane's diene **1** (1 M in benzene) following method B for 2 h (eluent hexane:EtOAc 95:5) as an orange solid in 38% yield; mp 114–115°C (hexane); $[\alpha]_D^{20} = -185$ (*c* 0.2, $CHCl_3$), ee >97% [Yb(hfc)$_3$]; ^{1}H NMR: δ 7.37 (d, 1H, J = 8.5 Hz), 6.75 (dd, 1H, J = 8.5 Hz and 2.4 Hz), 6.65 (d, 1H, J = 2.4 Hz), 6.59 (q, 1H, J = 1.6 Hz), 5.98–5.92 (m, 1H), 3.80 (s, 3H), 3.54–3.37 (m, 1H), 3.31–2.81 (m, 4H), 2.51–2.35 (m, 1H), 2.07 (d, 3H, J = 1.6 Hz), 1.69–1.50 (m, 1H); ^{13}C NMR: δ 187.4, 187.2, 159.1, 146.0, 141.7, 139.1, 137.4, 134.8, 128.7, 128.7, 125.3, 113.1, 112.5, 111.3, 55.2, 35.0, 31.5, 30.31, 25.2, 15.8; IR ν_{max}: 2990, 2940, 1650, 1600, 1130. Anal. calcd for $C_{20}H_{18}O_3$: C, 78.40; H, 5.93. Found: C, 78.28; H, 5.82.

5.12. 8-Methoxy-3-methyl-5,6-dihydro-1,4-chrysenequinone **12**

Compound **12** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5** and Dane's diene **1** (1 M in benzene) following method B for 2 h (eluent hexane:EtOAc 95:5) as a red solid in 22% yield; mp 181–182°C (hexane); ^{1}H NMR: δ 8.05 and 7.95 (AB system, 2H, J = 8.2 Hz), 7.67 (d, 1H, J = 8.6 Hz), 6.89 (dd, 1H, J = 8.6 and 2.7 Hz), 6.80 (d, 1H, J = 2.7 Hz), 6.78 (q, 1H, J = 1.6 Hz), 3.87 (s, 3H), 3.50 and 2.81 (2dd, 4H, J = 7.0 and 7.5 Hz), 2.19 (d, 3H, J = 1.6 Hz); ^{13}C NMR: δ 188.2, 184.8, 160.4, 149.7, 141.2, 139.7, 137.6, 136.5, 134.3, 131.6, 130.1 127.6, 126.2, 126.0, 125.4, 112.9, 55.3, 28.6, 25.6, 16.9; IR ν_{max}: 3020, 2920, 1655, 1610, 1130; EI-MS: m/z (%) 304 (M^+, 100), 275 (7), 261 (26), 202 (8), 163 (8), 149 (11); HRMS (EI) calcd for $C_{20}H_{16}O_3$: 304.10995; found: 304.10915.

5.13. (5R*)-6-(tert-Butyldimethylsilyloxy)-5-methyl-5,8-dihydro-1,4-naphthoquinone **13**

Compound **13** was obtained from (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**4** and (*Z*)-3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene **2** following method A at −20°C for 48 h (eluent

hexane:acetone 95:5) as a yellow oil in 32% yield; $[\alpha]_D^{20}=0$ (*c* 0.75, $CHCl_3$); ^1H NMR: δ 6.72 (s, 2H), 4.81 (dd, 1H, $J=3.0$ and 4.0 Hz), 3.4–2.9 (m, 3H), 1.27 (d, 3H, $J=6.8$ Hz), 0.94 (s, 9H), 0.18 and 0.17 (2s, 6H); ^{13}C NMR: δ 187.1, 186.6, 152.0, 143.9, 139.3, 136.7, 130.1, 96.7, 33.3, 25.6 (3C), 24.7, 19.6, 18.0, −4.5 (2C).

5.14. (5S)-6-(tert-Butyldimethylsilyloxy)-5-methyl-5,8-dihydro-1,4-naphthoquinone (−)-13

Compound (−)-**13** was obtained from (S*S*)-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**4** and (*Z*)-3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene **2** following method B for 1.5 h (eluent hexane:acetone 95:5) as a yellow oil in 36% yield; $[\alpha]_D^{20}=-49$ (*c* 0.18, $CHCl_3$), ee = 70% [$Pr(hfc)_3$].

5.15. (5R)-6-(tert-Butyldimethylsilyloxy)-2,5-dimethyl-5,8-dihydro-1,4-naphthoquinone (+)-14

Compound (+)-**14** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5** and (*Z*)-3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene **2** following method A at −20°C for 48 h, after separation of the 50:50 mixture of **14** and **15** (eluent CH_2Cl_2:hexane 50:50) as a yellow oil in 32% yield; $[\alpha]_D^{20}=+28$ (*c* 0.84, $CHCl_3$), ee = 78% [$Pr(hfc)_3$]; ^1H NMR: δ 6.55 (q, 1H, $J=1.6$ Hz), 4.80 (dd, 1H, $J=2.2$ and 4.7 Hz), 3.4–2.9 (m, 3H), 2.03 (d, 3H, $J=1.6$ Hz), 1.25 (d, 3H, $J=6.7$ Hz), 0.94, (s, 9H), 0.17 and 0.16 (2s, 6H); ^{13}C NMR: δ 187.6, 186.7, 151.9, 145.2, 143.6, 139.1, 133.5, 97.0, 33.2, 25.6 (3C), 24.8, 19.7, 18.0, 15.7, −4.5 (2C); IR ν_{max}: 2960, 2840, 2770, 1675, 1640, 1290, 1195, 855, 840; EI-MS: *m*/*z* (%) 318.2 (M^+, 36), 303 (11), 259 (100), 233 (34), 217 (5.9), 69 (40); HRMS (EI) calcd for $C_{18}H_{26}O_3Si$: 318.16512; found: 318.16548.

5.16. (8S)-7-(tert-Butyldimethylsilyloxy)-2,8-dimethyl-5,8-dihydro-1,4-naphthoquinone (−)-15

Compound (−)-**15** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5** and (*Z*)-3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene **2** following method A at −20°C for 48 h after separation of the 50:50 mixture of **15** and **14**, or following method B for 15 min (eluent CH_2Cl_2:hexane 50:50) as a yellow oil, in 20% yield (method A) or 42% yield (method B); $[\alpha]_D^{20}=-29$ (*c* = 0.4, $CHCl_3$), ee = 72% [$Pr(hfc)_3$]; ^1H NMR: δ 6.54 (q, 1H, $J=1.6$ Hz), 4.80 (dd, 1H, $J=3.0$ and 4.2 Hz), 3.4–2.9 (m, 3H), 2.05 (d, 3H, $J=1.6$ Hz), 1.25 (d, 3H, $J=6.7$ Hz), 0.94 (s, 9H), 0.17 and 0.16 (2s, 6H); ^{13}C NMR: δ 187.1, 187.0, 152.1, 145.8, 143.8, 139.2, 132.9, 97.0, 33.4, 25.7 (3C), 24.5, 19.6, 18.0, 15.8, −4.5 (2C); IR ν_{max}: 2940, 2920, 2840, 1675, 1640, 1270, 1175, 880, 865; EI-MS: *m*/*z* (%) 318.2 (M^+, 42), 303 (13), 259 (100), 233 (32), 69 (54); HRMS (EI) calcd for $C_{18}H_{26}O_3Si$: 318.16512; found: 318.16490.

5.17. (5R)-6-(tert-Butyldimethylsilyloxy)-2-isopropyl-5-methyl-5,8-dihydro-1,4-naphthoquinone (+)-16

Compound (+)-**16** was obtained from (S*S*)-2-isopropyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone[20] (+)-**6** and (*Z*)-3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene **2** following method A at −20°C for 56 h, after separation of the 80:20 mixture of **16** and **17** (eluent CH_2Cl_2:hexane 50:50) as a yellow oil in 40% yield; $[\alpha]_D^{20}=+49$ (*c* 0.8, $CHCl_3$), ee >97% [$Pr(hfc)_3$]; ^1H NMR: δ 6.48 (d, 1H, $J=1.2$ Hz), 4.81 (dd, 1H, $J=2.9$ and 4.4 Hz), 3.4–2.9 (m, 4H), 1.26 (d, 3H, $J=6.7$ Hz), 1.13 and 1.11 (2d, 6H, $J=7.0$ Hz), 0.94 (s, 9H), 0.17 and 0.16 (2s, 6H); ^{13}C NMR: δ 187.2, 186.8, 154.3, 151.9, 143.1, 139.4, 130.4, 97.1, 33.1, 26.6, 25.6 (3C), 24.9, 21.4 (2C), 19.6, 18.0, −4.6 (2C).

*5.18. (8S)-7-(*tert*-Butyldimethylsilyloxy)-2-isopropyl-8-methyl-5,8-dihydro-1,4-naphthoquinone (−)-**17***

Compound (−)-**17** was obtained from (S*S*)-2-isopropyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**6** and (*Z*)-3-(*tert*-butyldimethylsilyloxy)-1,3-pentadiene **2** following method A at −20°C for 56 h after separation of the 20:80 mixture of **17** and **16**, or following method B for 1 h (eluent CH_2Cl_2:hexane 50:50) as a yellow oil, in 10% yield (method A) or 62% yield (method B); $[\alpha]_D^{20}=-46$ (*c* 0.8, $CHCl_3$), ee = 74% [Pr(hfc)$_3$]; ^{1}H NMR 6.47 (d, 1H, $J=1.2$ Hz), 4.78 (dd, 1H, $J=2.9$ and 4.4 Hz), 3.4–2.9 (m, 4H), 1.26 (d, 3H, $J=6.6$ Hz), 1.12 (d, 6H, $J=6.8$ Hz), 0.94 (s, 9H), 0.18 and 0.16 (2s, 6H); ^{13}C NMR 187.6, 186.3, 155.0, 152.1, 144.0, 138.5, 129.7, 96.8, 33.4, 26.6, 25.6 (3C), 24.5, 21.5, 21.4, 19.6, 18.0, −4.5 (2C).

*5.19. (5S,8R)-6-(*tert*-Butyldimethylsilyloxy)-2,5-dimethyl-5,8-ethane-5,8-dihydro-1,4-naphthoquinone (−)-**18***

Compound (−)-**18** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5** and 2-(*tert*-butyldimethylsilyloxy)-1-methyl-1,3-cyclohexadiene **3** following method A at −20°C for 24 h, after separation of the 75:25 mixture of **18** and **19** (eluent hexane:acetone 95:5) as a yellow oil in 37% yield; $[\alpha]_D^{20}=-67$ (*c* 0.39, $CHCl_3$), ee >97% [Pr(hfc)$_3$]; ^{1}H NMR: δ 6.32 (q, 1H, $J=1.6$ Hz), 5.13 (d, 1H, $J=6.9$ Hz), 4.13 (dt, 1H, $J=6.9$ and 2.4 Hz), 1.99 (d, 3H, $J=1.6$ Hz), 1.72 (s, 3H), 1.7–1.3 (m, 4H), 0.92 (s, 9H), 0.10 and 0.07 (2s, 6H); ^{13}C NMR: δ 185.4, 184.7, 160.7, 152.1, 147.1, 143.1, 133.8, 102.7, 46.9, 35.0, 32.8, 26.6, 25.7 (3C), 18.2, 17.4, 15.2, −3.2, −3.6.

*5.20. (5R,8S)-7-(*tert*-Butyldimethylsilyloxy)-2,8-dimethyl-5,8-ethane-5,8-dihydro-1,4-naphthoquinone (+)-**19***

Compound (+)-**19** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5** and 2-(*tert*-butyldimethylsilyloxy)-1-methyl-1,3-cyclohexadiene **3** following method B for 3 h after separation of the 10:90 mixture of **19** and **20** as a yellow oil in 7% yield; $[\alpha]_D^{20}=+23$ ($c=0.47$, $CHCl_3$), ee = 78% [Pr(hfc)$_3$]; ^{1}H NMR: δ 6.40 (q, 1H, $J=1.6$ Hz), 5.12 (d, 1H, $J=6.9$ Hz), 4.10 (dt, 1H, $J=6.9$ and 2.8 Hz), 1.99 (d, 3H, $J=1.6$ Hz), 1.74 (s, 3H), 1.68–1.34 (m, 4H), 0.92 (s, 9H), 0.11 and 0.08 (2s, 6H); ^{13}C NMR: δ 185.6, 184.3, 160.7, 152.1, 147.2, 146.1, 131.0, 102.5, 47.0, 32.4, 26.6, 25.7, 18.2, 17.6, 16.1, 3.6, 3.2; IR ν_{max}: 2920, 2840, 1525, 1015, 990; EI-MS: *m*/*z* (%) 316 (M^+−28, 10), 259 (100), 225 (71), 167 (8), 149 (26), 84 (82).

*5.21 5a-(*tert*-Butyldimethylsilyloxy)-4,9a-dimethyl-1-(*p*-tolylsulfinyl)-5a,8,9,9a-tetrahydrodibenzofuran-2-ol **20***

Compound **20** was obtained from (S*S*)-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**5** and 2-(*tert*-butyldimethylsilyloxy)-1-methyl-1,3-cyclohexadiene **3** following method B for 3 h after separation of the 90:10 mixture of **20** and **19** as an inseparable 60:40 mixture of diastereoisomers in 56% yield; ^{1}H NMR (major): δ 9.75 (s, 1H, O*H*), 7.50 and 7.24 (AA′BB′ system, 4H), 6.59 (broad s, 1H), 6.1–5.6 (m, 2H), 2.38 (s, 3H), 2.2–1.8 (m, 2H), 1.6–1.2 (m, 2H), 1.16 (s, 3H), 0.78 (s, 9H), 0.21 and −0.06 (2s, 6H); (minor): δ 9.98 (s, 1H), 7.60 and 7.28 (AA′BB′ system, 4H), 6.62 (broad s, 1H), 6.1–5.6 (m, 2H), 2.38 (s, 3H), 2.2–1.8 (m, 2H), 1.6–1.2 (m, 2H),

1.48 (s, 3H), 0.84 (s, 9H), 0.23 and −0.06 (2s, 6H); IR ν_{max}: 3660, 2915, 1840, 1620, 1595, 1460, 1420, 1180, 1120; EI-MS: m/z (%) 484 (M^+, 52), 468 (28), 427 (26), 411 (42), 345 (24), 287 (20), 149 (11), 91 (21), 75 (36); HRMS (EI) calcd for $C_{27}H_{36}O_4SSi$: 484.72500; found: 484.72485.

*5.22. (5*S*,8*R*)-6-(*tert*-Butyldimethylsilyloxy)-2-isopropyl-5-methyl-5,8-ethane-5,8-dihydro-1,4-naphthoquinone (−)-**22***

Compound (−)-**22** was obtained from (S*S*)-2-isopropyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**6** and 2-(*tert*-butyldimethylsilyloxy)-1-methyl-1,3-cyclohexadiene **3** following method A at rt for 18 h, after separation of the 94:6 mixture of **22** and **23** (eluent hexane:acetone 95:5) as a yellow solid in 40% yield; mp 88–89°C (hexane:ethyl ether); $[\alpha]_D^{20} = -51$ (c 0.65, $CHCl_3$), ee = 84% [Pr(hfc)$_3$]; ^{1}H NMR: δ 6.24 (d, 1H, J = 1.1 Hz), 5.14 (d, 1H, J = 7.0 Hz), 4.14 (dt, 1H, J = 7.0 and 2.2 Hz), 3.00 (dsept, 1H, J = 1.1 and 7.0 Hz), 1.72 (s, 3H), 1.7–1.3 (m, 4H), 1.11 and 1.08 (2d, 6H, J = 7.0 Hz), 0.92 (s, 9H), 0.10 and 0.08 (2s, 6H); ^{13}C NMR: δ 185.9, 184.0, 160.7, 152.4, 152.2, 146.7, 130.9, 102.7, 46.8, 35.0, 32.9, 26.6, 26.3, 25.7 (3C), 21.6, 21.4, 18.1, 17.4, 15.2, −3.2, −3.7. Anal. calcd for $C_{22}H_{32}O_3Si$: C, 70.93; H, 8.66. Found: C, 71.08; H, 8.82.

*5.23. (5*R*,8*S*)-7-(*tert*-Butyldimethylsilyloxy)-2-isopropyl-8-methyl-5,8-ethane-5,8-dihydro-1,4-naphthoquinone **23***

Compound **23** was obtained from (S*S*)-2-isopropyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**6** and 2-(*tert*-butyldimethylsilyloxy)-1-methyl-1,3-cyclohexadiene **3** following method A at rt for 18 h, after purification of the 6:94 mixture of **23** and **22** (eluent hexane:acetone 95:5). The following data for **23** were taken from a 22:78 mixture of **23** and **22**; ee = 82% [Pr(hfc)$_3$]; ^{1}H NMR: δ 6.33 (d, 1H, J = 1.2 Hz), 5.14 (d, 1H, J = 6.9 Hz), 4.13–4.07 (m, 1H), 3.01 (dsept, 1.2 and 7.0 Hz), 1.74 (s, 3H), 1.6–1.2 (m, 4H), 1.11 and 1.04 (2d, 6H, J = 7.0 Hz), 0.93 (s, 9H), 0.10 and 0.09 (2s, 6H); ^{13}C NMR: δ 185.0, 184.8, 160.8, 155.2, 151.4, 147.5, 127.9, 102.8, 47.2, 35.1, 32.4, 30.9, 26.5, 25.6 (3C), 21.8, 21.6, 18.2, 17.6, −3.2, −3.6 (2C).

*5.24. 5a-(*tert*-Butyldimethylsilyloxy)-4-isopropyl-9a-methyl-1-(*p*-tolylsulfinyl)-5a,8,9,9a-tetrahydrodibenzofuran-2-ol **24***

Compound **24** was obtained from (S*S*)-2-isopropyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-**6** and 2-(*tert*-butyldimethylsilyloxy)-1-methyl-1,3-cyclohexadiene **3** following method B for 4 h, as an inseparable 60:40 mixture of diastereoisomers in 51% yield; ^{1}H NMR (major): δ 9.82 (s, 1H), 7.50 and 7.27 (AA′BB′ system, 4H), 6.67 (s, 1H), 5.93 and 5.69 (2dt, 2H, J = 10.0 and 4.1 Hz; J = 10.0 and 1.6 Hz), 3.04 (m, 1H), 2.40 (s, 3H), 2.2–1.9 (m, 2H), 1.8–1.4 (m, 2H), 1.20 and 1.16 (2d, 6H, J = 7.0 Hz), 1.15 (s, 3H), 0.81 (s, 9H), 0.23 and 0.06 (2s, 6H); (minor): δ 10.10 (s, 1H), 7.64 and 7.28 (AA′BB′ system, 4H), 6.71 (s, 1H), 5.72 and 5.63 (2dt, 2H, J = 10.0 and 4.1 Hz; J = 10.0 and 1.6 Hz), 3.04 (m, 1H), 2.41 (s, 3H), 2.2–1.9 (m, 2H), 1.8–1.4 (m, 2H), 1.48 (s, 3H), 1.21 and 1.17 (2d, 6H, J = 7.0 Hz), 0.88 (s, 9H), 0.25 and 0.09 (2s, 6H).

Acknowledgements

We thank Dirección General de Investigación Científica y Técnica (grants PB98-0062 to MCC and PB98-0078 to JLGR) for financial support. CZR thanks Ministerio de Educación y Ciencia: Programa de Cooperación con Iberoamérica for a fellowship.

References

1. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: New York, 1990; pp. 61–72.
2. For general reviews on asymmetric Diels–Alder reactions, see: (a) Oppolzer, W. In *Comprehensive Organic Syntheses*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp. 315–399. (b) Taschner, M. J. In *Asymmetric Diels–Alder Reactions*; Taschner, M. J., Ed.; JAI Press: Greenwich, 1989; Vol. 1, pp. 1–101.
3. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley: New York, 1978.
4. (a) Dickinson, R. A.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1972**, *50*, 2377–2380. (b) Das, J.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308–3319. (c) Tou, J. S.; Reusch, W. *J. Org. Chem.* **1980**, *45*, 5013–5015. (d) Quinkert, G.; Grosso, M.; Bucher, A.; Bats, J. W. *Tetrahedron Lett.* **1991**, *32*, 3357–3360. (e) Arseniyadis, S.; Rodríguez, R.; Spanevello, R.; Cámara, J.; Thompson, A.; Guittet, E.; Ourisson, G. *Tetrahedron* **1992**, *48*, 1255–1262. (f) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 1909–1910. (g) Quinkert, G.; Grosso, M.; Bucher, A.; Bauch, M.; Doring, W.; Bats, J. W.; Durner, G. *Tetrahedron Lett.* **1992**, *33*, 3617–3620. (h) Arseniyadis, S.; Rodríguez, R.; Yashunsky, D. V.; Cámara, J.; Ourisson, G. *Tetrahedron Lett.* **1994**, *35*, 4843–4846.
5. For an overview, see: (a) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760. (b) García Ruano, J. L.; Carretero, J. C.; Carreño, M. C.; Martín Cabrejas, L. M.; Urbano, A. *Pure Appl. Chem.* **1996**, *68*, 925–930.
6. (a) Carreño, M. C.; García Ruano, J. L.; Toledo, M. A.; Urbano, A.; Remor, C. Z.; Stefani, V.; Fischer, J. *J. Org. Chem.* **1996**, *61*, 503–509. (b) Carreño, M. C.; García Ruano, J. L.; Lafuente, C.; Toledo, M. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1119–1128. (c) Carreño, M. C.; García Ruano, J. L.; Urbano, A.; Remor, C. Z.; Arroyo, Y. *J. Org. Chem.* **2000**, *65*, 453–458.
7. (a) Carreño, M. C.; Urbano, A.; Fischer, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1621–1623. (b) Carreño, M. C.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **1998**, *63*, 8320–8330. (c) Carreño, M. C.; Urbano, A.; Di Vitta, C. *Chem. Commun.* **1999**, 817–818. (d) Carreño, M. C.; García Ruano, J. L.; Toledo, M. A. *Chem. Eur. J.* **2000**, *6*, 288–291. (e) Carreño, M. C.; Urbano, A.; Di Vitta, C. *Chem. Eur. J.* **2000**, *6*, 906–913.
8. (a) Carreño, M. C.; García-Cerrada, S.; Urbano, A.; Di Vitta, C. *Tetrahedron: Asymmetry* **1998**, *9*, 2965–2969. (b) Carreño, M. C.; García-Cerrada, S.; Urbano, A.; Di Vitta, C. *J. Org. Chem.* **2000**, *65*, 4355–4363.
9. Carreño, M. C.; García Ruano, J. L.; Urbano, A. *J. Org. Chem.* **1992**, *57*, 6870–6876.
10. 1,2-Dialkylsubstituted dienes, see references 4c,e,h and the following: (a) Kolaczkowski, L.; Reusch, W. *J. Org. Chem.* **1985**, *50*, 4766–4771. (b) De Riccardis, F.; Izzo, I.; Di Filippo, M.; Sodano, G.; D'Acquisto, F.; Canuccio, R. *Tetrahedron* **1997**, *53*, 10871–10882.
11. Dane's diene, see references 4a,b,d,g and the following: (a) Cole, J. E.; Johnson, W. S.; Robin, P. A. *J. Chem. Soc.* **1962**, 244–278. (b) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 637–740. (c) Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron Lett.* **1992**, *33*, 1909–1910. (d) Alonso, I.; Carretero, J. C.; García Ruano, J. L.; Martín Cabrejas, L. M.; López-Solera, I.; Raithby, R. *Tetrahedron Lett.* **1994**, *35*, 9461–9464. (e) Quinkert, G.; Grosso, M.; Döring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1995**, *78*, 1345–1391. (f) Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 7403–7406. (g) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697–1701.
12. 1-Alkyl-2-alkoxysubstituted dienes: (a) Sarett, L. H.; Lukes, R. M.; Poos, G. I.; Robinson, J. M.; Beyler, R. E.; Vandegrift, J. M.; Arth, G. E. *J. Am. Chem. Soc.* **1952**, *74*, 1393–1397. (b) Beyer, R. E.; Sarett, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 1397–1401. (c) Schmidt, C.; Sabnis, S. D.; Schmidt, E.; Taylor, D. K. *Can. J. Chem.* **1971**, *49*, 371–374. (d) Bohlmann, F.; Förster, H. J.; Fischer, C. H. *Liebigs Ann. Chem.* **1976**, 1487–1513. (e) Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1977**, *25*, 2535–2544. (f) Mock, G. A.; Holmes, A. B.; Raphael, R. A. *Tetrahedron Lett.* **1977**, 4539–4540. (g) Yamakawa, K.; Satoh, T. *Chem. Pharm. Bull.* **1979**, *27*, 1747–1752. (h) Danishefsky, S.; Kahn, M. *Tetrahedron Lett.* **1981**, *22*, 489–492. (i) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460–3467. (j) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400–406.
13. (a) Dane, E.; Schmitt, J. *Liebigs Ann. Chem.* **1938**, *536*, 196. (b) Dane, E.; Schmitt, J. *Liebigs Ann. Chem.* **1939**, *537*, 246. (c) Robins, P. A.; Walker, J. *J. Chem. Soc.* **1956**, 3249.
14. Carreño, M. C.; García Ruano, J. L.; Remor, C. Z.; Urbano, A.; Fischer, J. *Tetrahedron Lett.* **1997**, *38*, 9077–9080.
15. See reference 13 and the following: (a) Hajos, Z. H.; Parrish, D. R.; Goldberg, M. W. *J. Org. Chem.* **1965**, *30*, 1213–1222. (b) Symmes, C.; Quin, L. D. *J. Org. Chem.* **1979**, *44*, 1048–1056.

16. (a) Jacobi, P. A.; Cai, G. *Heterocycles* **1993**, *35*, 1103–1120. (b) Nakagawa, M.; Arisawa, M.; Torisawa, Y. *Synthesis* **1995**, 1371–1372.
17. Evans, P. A.; Nelson, J. D. *J. Org. Chem.* **1996**, *61*, 7600–7602.
18. Koo, S.; Chong, B. D.; Oh, S. S.; Yang, J. D.; Baik, W. *J. Org. Chem.* **1997**, *62*, 9323–9325.
19. Carreño, M. C.; García Ruano, J. L.; Urbano, A. *Synthesis* **1992**, 651–653.
20. Carreño, M. C.; García Ruano, J. L.; Toledo, M. A.; Urbano, A. *Tetrahedron: Asymmetry* **1997**, *8*, 913–921 and 1337.
21. This *meta*-adduct refers to the C-1 substituent of the diene. Taking the C-2 substituent of the diene as reference, this is the *para*-adduct.
22. Claridge, T. D. W. *High-Resolution NMR Techniques in Organic Chemistry*; Elsevier: New York, 1999; Chapter 6.
23. For recent references, see: (a) Fariña, F.; Paredes, M. C.; Valderrama, J. *Tetrahedron* **1992**, *48*, 4629–4640. (b) Brimble, M. A.; Elliot, R. J. R. *Tetrahedron*, **1997**, *53*, 7715–7730. (c) Engler, T. A.; Letavic, M. A.; Iyengar, R.; LaTessa, K. O.; Reddy, J. P. *J. Org. Chem.* **1999**, *64*, 2391–2405. (d) Carreño, M. C.; García Ruano, J. L.; Urbano, A.; Remor, C. Z.; Arroyo, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 4357–4367 and references cited therein.