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Stereocontrolled Approach to Phenyl Cyclitols from (*SR*)-[(*p*-Tolylsulfinyl)methyl]-*p*-quinol

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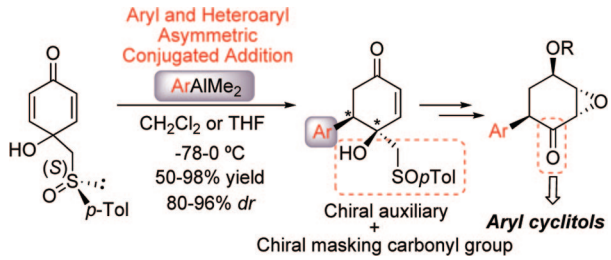

Reactions of enantiopure (*SR*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinol with $ArAlMe_2$ reagents allowed a highly diastereoselective 1,4-addition of the aryl group with an efficient desymmetrization of the prochiral cyclohexadienone moiety. The asymmetric synthesis of phenyl-substituted polyoxygenated cyclohexane derivatives was achieved by combining this reaction with a stereoselective reduction and elimination of the β-hydroxysulfoxide, after oxidation to sulfone, to recover a carbonyl group, and a stereoselective epoxidation.

Introduction

Asymmetric conjugate additions have been efficiently achieved by using chiral electrophiles, nucleophiles,[1] and chiral catalysts,[1,2] including metal catalysts[3] and organocatalysts.[4] Extensive studies have been devoted to 1,4-addition of alkyl organometallic reagents. When dealing with aryl organometallics, high stereoselectivities can be achieved upon reactions of aryl lithium reagents with enoates in the presence of enantiopure ligands[5] or with homochiral vinyl sulfoximines as the acceptor.[6] Rhodium-catalyzed 1,4-addition of aryl boronic acids to enones in the presence of chiral ligands is nowadays recognized as an efficient method to form C-aryl bonds with high enantioselectivity.[7] The synthesis of 3-aryl-substituted ketones was achieved by Knochel through a copper-catalyzed process using functionalized arylmagnesium compounds generated by metalation of arylhalides by isopropyl magnesium chloride in the presence of lithium chloride.[8] Westermann[9] reported in 1998 the nickel-catalyzed 1,4-addition of aryl dialkyl aluminum reagents to

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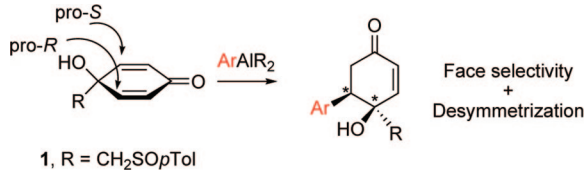
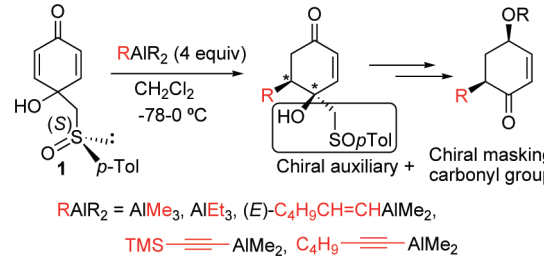
SCHEME 1. 4-Hydroxy-4-Substituted 2,5-Cyclohexadienones as Starting Materials in Asymmetric Synthesis



enones en route to 3-aryl ketones. The procedure was applied to trisubstituted enones and allowed the access to quaternary centers at the β-position. More recently, Alexakis[10] reported the enantioselective copper-catalyzed 1,4-aryl transfer of arylaluminum reagents to trisubstituted cyclic enones in the presence of chiral phosphoramidite ligands, leading to quaternary stereocenters. In spite of the advances reached, the stereoselective introduction of alkyl or aryl groups to symmetrically 4,4-disubstituted cyclohexadienones or 4-hydroxy-4-alkyl-substituted cyclohexadienones (*p*-quinols) remains a challenge in asymmetric synthesis due to the symmetry of such prochiral moieties, where up to four diastereomers can be formed during the conjugate addition. The stereoselective differentiation of the two diastereotopic conjugate positions (pro-*R* and pro-*S*) and the two different faces for each conjugate attack poses a challenging problem whose efficient solution is of huge synthetic interest due to the multifunctional nature and potential synthetic utility of the *p*-quinol unit (Scheme 1).[11]

Efficient desymmetrizations of cyclohexadienone moieties have only been achieved by Feringa,[12] using a BINOL phosphoramidite ligand, in the Cu-catalyzed enantioselective 1,4-additions of dialkyl zinc derivatives to *p*-benzoquinone monoketals and 4-alkoxy-4-alkyl-substituted cyclohexadienones. We have found that (*SR*)-[(*p*-tolylsulfinyl)methyl]-*p*-quinol derivatives such as **1**, bearing a CH_2-sulfoxide substituent at C-4,[13] reacted with organoaluminum reagents (alkyl, alkenyl, or alkynyl), leading to the exclusive formation of 1,4-conjugate addition products in the absence of any other metal catalyst,[14] in a highly chemo- and π-facial diastereoselective manner (Scheme 2). The efficient desymmetrization of the prochiral dienone moiety, reacting exclusively from the pro-*S* double bond *syn* to the face containing the C-4 OH, allowed the controlled formation of two stereogenic centers in a single step. Furthermore, we observed that the β-hydroxysulfoxide present in the resulting 1,4-adducts could be regarded as a chiral equivalent of a ketone, which can be recovered after oxidation to sulfone

SCHEME 2. Conjugate Additions on Enantiopure 4-Hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone (*SR*)-1 and Applications in Asymmetric Synthesis



and mild basic treatment.[15] Both findings allowed us to synthesize different chiral nonracemic alkyl hydroxy-substituted cyclohexenones such as phorenol,[15] as well as different natural polyoxygenated cyclohexane derivatives[16] and C-4 oxygenated angucyclinones.[17]

Despite the rich latent functionality of enantiopure cyclohexadienones, they had never been used for the synthesis of aryl-substituted polyhydroxycyclohexane derivatives,[18,19] probably due to the lack of efficient desymmetrization methods, allowing the introduction of aryl nucleophiles to the *p*-quinols in a conjugate and stereoselective manner. The efficient construction of such derivatives is of huge interest since these moieties are present in a group of natural products, the *Amaryllidaceae* family and analogues[20] that show important biological properties, including anticancer activity. The potential usefulness of *p*-quinols as starting materials for such interest chiral targets prompted us to extend the scope of the conjugated additions of 4-[(*p*-tolylsulfinyl)methyl]-*p*-quinols to aryl organometallics. We now report our results evidencing that the remote sulfoxide is able to direct the reaction of **1** with aryl organoaluminum reagents, leading to the 1,4-conjugate addition products in a stereocontrolled manner without adding any catalyst. C-aryl-substituted polyoxygenated cyclohexanes were obtained by further transforming the initial 1,4-adducts through a series of stereoselective reactions and the elimination of the β-hydroxysulfoxide, after oxidation to sulfone, to recover a ketone. The overall sequence can be regarded as an umpolung

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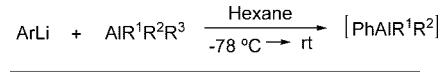
SCHEME 3. Synthesis of Phenyl Organoaluminum Reagents



entry	ArLi (equiv)	$AlR^1R^2R^3$	$[PhAlR^1R^2]$
1	PhLi (3)	$AlCl_3$	$[Ph_3Al]$
2	PhLi (2)	$MeAlCl_2$	$[Ph_2AlMe]$
3	PhLi (1)	Me_2AlCl	$[PhAlMe_2]$

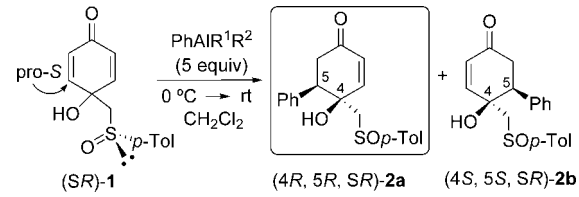
α-arylation of the keto group recovered after the elimination of methyl *p*-tolylsulfone.

Results and Discussion

Enantiopure [(*p*-tolylsulfinyl)methyl]-*p*-quinol (*SR*)-**1** was synthesized from (*SR*)-methyl *p*-tolyl sulfoxide and *p*-benzoquinone dimethyl monoketal, as previously described.[21] We initially focused in the asymmetric conjugate addition of a phenyl group. Reactions of *p*-quinols[22,23] and their ethers[22,24] with alkyl organometallic reagents had been shown to give mixtures of 1,2- and 1,4-addition products, depending on the nature of the reagent and/or the presence of the free OH in the cyclohexadienone. In light of this background and our findings on alkyl organoaluminum conjugated additions,[13,25,26] we first explored the reactivity of *p*-quinol **1** with phenyl alanes. Triphenyl aluminum can be easily prepared by the addition of a commercially available solution of PhLi (2.0 M in dibutylether, 3 equiv) over a suspension of $AlCl_3$ in hexane at −78 °C to rt (table in Scheme 3, entry 1).[27] On the basis of the work by Westermann,[9] we envisaged also generating other phenyl aluminum reagents, such as methyldiphenyl aluminum (Ph_2AlMe) or dimethylphenyl aluminum reagent ($PhAlMe_2$). Both alanes can be easily prepared by treating a solution of $MeAlCl_2$ or $AlMe_2Cl$ in hexane with PhLi (2 or 1 equiv, respectively) (see table in Scheme 3, entries 2 and 3).

Freshly prepared phenyl organoaluminum reagents were directly used in the reaction with *p*-quinol **1**. We first tested the behavior of Ph_3Al. Taking into account the presence of the free OH in the *p*-quinol **1**, we used an excess of Ph_3Al (5 equiv). When a solution of **1** in CH_2Cl_2 was added over freshly prepared Ph_3Al at 0 °C, no reaction was observed, even after leading the reaction mixture to warm to room temperature (table in Scheme 4, entry 1). The use of THF instead of CH_2Cl_2 did not give the addition product either. By adding a solution of **1** in CH_2Cl_2 over Ph_2AlMe under the conditions indicated in Scheme 4 (entry 2), the conjugate addition product **2** was formed with a conversion of 55% as a 75:25 mixture of diastereomers. The absolute configuration of the phenyl adducts was determined to be (4*R*,5*R*,*SR*)-**2a** and (4*S*,5*S*,*SR*)-**2b** (see below). The major diastereomer (4*R*,5*R*,*SR*)-**2a** resulted from the 1,4-transfer of the phenyl group from the organoaluminum reagent to the pro-*S* conjugate position *syn* to the face containing the hydroxyl substituent. We finally found that the reaction of **1** with $PhAlMe_2$, generated by transmetalation of PhLi (5 equiv) with $AlMe_2Cl$ (5 equiv), gave the 1,4-addition product (4*R*,5*R*,*SR*)-**2a** in a highly diastereoselective manner (dr: 96:4) and excellent yield (98% for the mixture of diastereomers) (table in Scheme 4, entry 3).

SCHEME 4. Reaction of Phenyl Organoaluminum Reagents with (*SR*)-1



entry	$PhAlR^1R^2$	*dr*: **2a/2b** (yield)
1	Ph_3Al	no reaction
2	Ph_2AlMe	75/25
3	**$PhAlMe_2$**	**96/4 (98%)**

It is worth mention that we did not observe the formation of the product resulting from the transfer of a methyl group.[28] The use of such a high excess of $PhAlMe_2$ was necessary for the rapid completion of the reaction since with 1 or 2 equiv the starting material remained unchanged and with 3 or 4 equiv the conversion was not complete. To disregard PhLi as the phenyl source in this reaction, we treated **1** with an excess of PhLi. Under the same reaction conditions, using CH_2Cl_2 as solvent and 5 equiv of PhLi, the *p*-quinol **1** was recovered unchanged. The 1,2-addition products were formed in a poorly stereoselective manner when the solvent for the PhLi addition was changed to THF. The high reactivity shown by the dimethylphenyl alane with our 4-hydroxy-4-[(*p*-tolylsulfinyl)-methyl]-substituted cyclohexadienone had been already observed for other alanes[13,15,16] as well as the need of an excess of the reagent to complete the 1,4-additions. The existence of the free OH at C-4 in these substrates had been previously shown to be essential to increase the otherwise poor reactivity of trialkylalanes in uncatalyzed conjugate additions.[13] In order to demonstrate the role of the OH in the conjugate addition of the phenyl aluminum reagent, we effected the reaction of 4-methoxy-substituted cyclohexadienone (*SR*)-**3**[13b] with $PhAlMe_2$ under the conditions used above (PhLi, $AlMe_2Cl$, 0 °C). As shown in Scheme 5, a mixture of diastereomers **4** and **5**,[29] resulting from 1,2-addition of the phenyl to the carbonyl group of **3**, was formed, from which both **4** and **5** could be isolated pure in 70 and 12% yield, respectively. The major diastereomer **4** resulted from the attack of the phenyl aluminum reagent from the face

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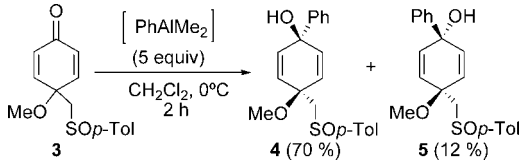
(28) Upon reaction with alkenyl or alkynyldimethylaluminum reagents, compound **1** gave 10−15% of the corresponding 5-methylcyclohexenone product; see ref 13.
(29) The stereochemistry of the minor carbinol **5** was unequivocally established by X-ray diffraction: CCDC 712061, M_r $C_{21}H_{22}O_3S$, unit cell parameters: a = 7.36750(10), b = 32.5836(6), c = 7.58820(10) Å, β = 101.6190(10)°, space group $P21$; see Supporting Information for details.

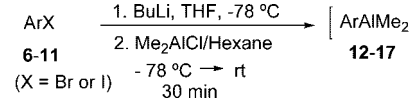
SCHEME 5. Reaction of Phenyl Dimethyl Aluminum with 3



of the carbonyl opposite to the one bearing the more electronegative OMe substituent at C-4. This stereoselectivity was not unexpected since precedent work by Wipf[30] had evidenced that remote dipolar interactions could control the π-facial diastereoselectivity of 1,2-additions on 4-alkoxy-substituted 2,5-cyclohexadienones. This result corroborates the essential role of the free OH directing the conjugate addition on the *p*-quinol **1**. It is worth mention that the analogue reaction of methoxy derivative **3** with commercially available $AlMe_3$ occurred much more slowly, with a conversion of only 10% after 4 h.[13b] The high reactivity observed when $PhAlMe_2$, generated from PhLi and $AlMe_2Cl$, was the reagent can be due to presence of LiCl in the reaction medium that could activate the cyclohexadienone acceptor. With the commercially available $AlMe_3$, the absence of salts could be in the origin of the decreased reactivity.

A possible mechanistic pathway explaining the chemo- and diastereoselective 1,4-addition of $PhAlMe_2$ on *p*-quinol (*SR*)-**1** is summarized Scheme 6. The stoichiometric addition of $PhAlMe_2$ led to an unreactive aluminum alkoxide **A**, where the metal is associated with the sulfinylic oxygen. Although this initial acid−base reaction could give two differently substituted aluminum alkoxides, the formation of **A** must be favored on the basis of the lower acidity of the conjugate acid lost (CH_4: pK_a ~55). This species, with a methyl and a phenyl substituent at the aluminum, has a frozen chairlike conformation due to the preferred equatorial disposition of the *p*-Tol and phenyl groups. In such an arrangement, the axial methyl substituent linked to the aluminum atom is hindering the pro-*R* double bond to any nucleophile approach from the face containing the alkoxide group and renders only the pro-*S* conjugate position available. This could be the origin of the diastereotopic group selection. The second alane equivalent, acting as a Lewis acid, should associate the carbonyl oxygen increasing the reactivity of the system (**B**). The use of an excess of aluminum reagent warrants the completion, due to the associated nature of the organoaluminum reagent,[31] that could retard the intramolecular transfer assisted by the alkoxide. A plausible explanation for the lack of reactivity observed in the case of Ph_3Al could be the unfavorable formation of an aluminum alkoxide similar to **A**, whose chairlike conformation has two bulky phenyl groups at the aluminum atom. The high π-facial diastereoselectivity directed by the OH could be expected considering the similar diastereoselective 1,4-addition found in Grignard additions to the lithium alkoxides of *p*-quinols in racemic series.[23]

Once the experimental conditions for the transfer of the Ph group from $PhAlMe_2$ were optimized, we decided to investigate if the process could be general enough to introduce a wide range of aryl and heteroaryl groups in the *p*-quinol **1**. The in situ transmetalation between an ArLi reagent and $AlMe_2Cl$ to produce the $ArAlMe_2$ required the previous formation of the ArLi when not commercially available. Such aryl or heteroaryl lithium reagents were generated by halogen−metal exchange between an aryl or heteroaryl halide and *n*-BuLi or by directed orthometalation from the adequately substituted aromatic precursor, depending on the availability of the starting material (eq 1).



(1)

The freshly prepared alane was directly used in the reaction with the *p*-quinol **1**. The results of the reactions with differently substituted aryl dimethyl aluminum reagents are indicated in Table 1. Starting from 4-trifluoromethyl bromobenzene **6**, the bromo-lithium exchange (*n*-BuLi, THF, −78 °C, 10 min) was followed by the addition of a hexane solution of Me_2AlCl (30 min). After evaporation of the solvents under vacuum, CH_2Cl_2 was added on the resulting aluminum reagent **12**, followed by a solution of (*SR*)-**1** in CH_2Cl_2 at 0 °C and then warming the reaction to room temperature. Under these conditions, a 60:40 mixture of diastereomers **18a** and **18b** was isolated in a poor 12% yield, which could not be improved even after long reaction times (Table 1, entry 1). This experimental protocol was applied to obtain all the aryl dimethyl aluminum reagents **13**−**17**. The *p*-quinol **1** was recovered unchanged when the aluminum reagent **13** was derived from *p*-nitrobromobenzene **7** (Table 1, entry 2). The poor yield obtained from the *p*-trifluoromethylphenyl-substituted alane **12** and the lack of reaction with *p*-nitrophenyl dimethyl aluminum **13** indicated that the electron-poor aryl groups were not nucleophilic enough to be efficiently transferred. Better results were obtained from *p*-methyl iodobenzene **8**, whose sequential treatment with *n*-BuLi and Me_2AlCl to generate the aluminum reagent **14**, followed by addition of the *p*-quinol **1**, afforded a 95:5 mixture of compounds **19a/19b**, which was isolated in a 60% yield (Table 1, entry 3). The major diastereomer **19a** also resulted from the 1,4-addition on the pro-*S* double bond of **1** from the face bearing the OH. A slightly lower selectivity was observed in the reaction of compound **1** with *p*-dimethylaminophenyl dimethyl aluminum **15** generated from *p*-dimethylamino bromobenzene **9**. A 90:10 mixture of diastereomers **20a/20b** resulted in 85% yield (Table 1, entry 4). The alkoxy-substituted aryl aluminum reagents **16** and **17** were formed from *p*-bromoanisol **10** and 3,4-methylenedioxy bromobenzene **11**, respectively, by sequential reaction with *n*-BuLi and Me_2AlCl. Their reaction with *p*-quinol **1** led to the 1,4-addition products **21** and **22** in 95:5 (**21a/21b**) and 75:25 (**22a/22b**) diastereomeric ratios (Table 1, entries 5 and 6). Taking into account the frequent presence of the methylenedioxyphenyl

SCHEME 6. Associated Species Explaining the High Site and Diastereofacial Selective 1,4-Addition

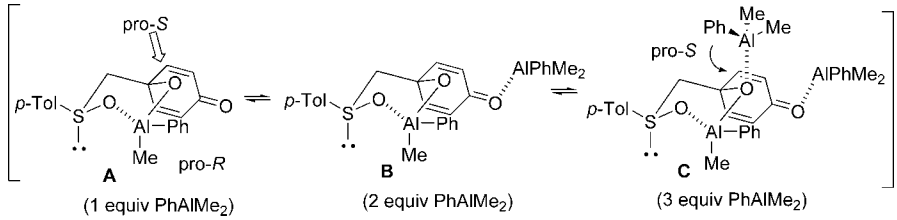
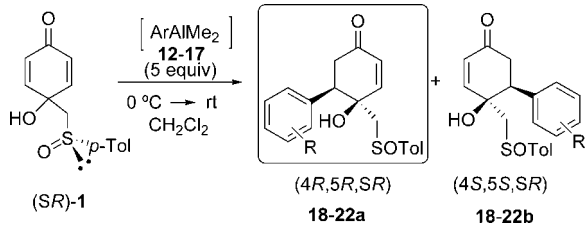


TABLE 1. Reactions of Aryldimethyl Aluminum Reagents with (*SR*)-*p*-Quinol 1[a]



entry	ArX (**6-11**)	[$ArAlMe_2$]	t (h)	**18-22 (a:b)**	yield (%)
1	F_3C–Br **6**	**12**	5	**18a**:**18b** (60:40)	12
2	O_2N–Br **7**	**13**	5	—	—
3	Me–I **8**	**14**	2	**19a**:**19b** (95:5)	60
4	Me_2N–Br **9**	**15**	1	**20a**:**20b** (90:10)	85
5	MeO–Br **10**	**16**	2	**21a**:**21b** (95:5)	50
6	Br **11**	**17**	3	**22a**:**22b** (75:25)	53
7	**11**	**17**	1.5	**22a**:**22b** (80:20)[a]	60

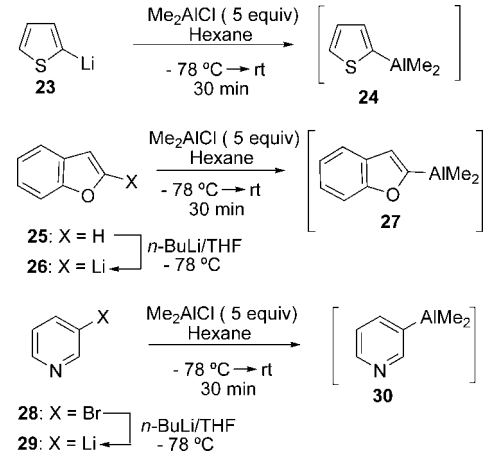
[a] THF was used as solvent.

moiety in the structure of natural products, we tried to improve the diastereoselectivity of the reaction of **1** with the aluminum reagent **17**. After different reactions at lower temperatures and different solvents, a slight improvement could only be achieved when the *p*-quinol **1**, dissolved in THF, was added to the previously generated aluminum reagent **17** (Table 1, entry 7, **22a/22b**, 80:20).

We also studied the behavior of heteroaryl dimethyl aluminum reagents **24**, **27**, and **30**, which were easily prepared by the addition of the corresponding heteroaryl lithium reagent to $AlMe_2Cl$ in hexane at −78 °C. A commercially available solution of 2-thienyl lithium **23** (1 M in THF, 5 equiv) was used for the preparation of dimethyl 2-thienyl aluminum **24** (5 equiv, hexane solution) (Scheme 7). 2-Benzofuranyl lithium reagent **26**, prepared by directed orthometalation of benzofuran **25** with *n*-BuLi in THF at −78 °C, was the precursor of 2-benzofuranyl dimethyl aluminum **27**, and the 3-pyridyl dimethyl aluminum **30** could be generated in two steps by halogen-lithium exchange between 3-bromopyridine **28** and *n*-BuLi followed by reaction of the resulting 3-lithiumpyridine **29** with $AlMe_2Cl$ (Scheme 7).

The results of the conjugate addition of the resulting heteroaryl alanes to **1** are shown in Table 2. In all cases, a solution of *p*-quinol (*SR*)-**1** in THF was added over a freshly prepared solution of the alane at 0 °C and then warming the reaction mixture to room temperature. Dimethyl 2-thienyl aluminum **24** gave the desired conjugate addition product as 80:20 mixture of diastereoisomers **31a** and **31b** in 90% yield (Table 2, entry 1). The conjugate addition of dimethyl 2-benzofuranyl aluminum **27** was completed within 2 h to give a

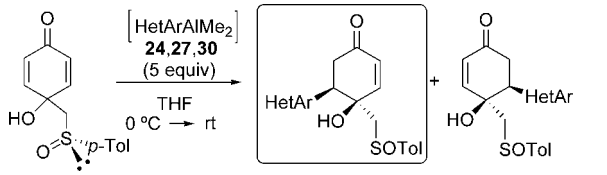
SCHEME 7. Preparation of Dimethyl Heteroaryl Aluminum Reagents 24, 27, and 30



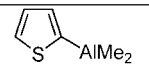
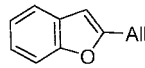
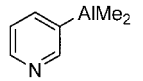
80:20 mixture of diastereomers **32a** and **32b** in a 75% yield (Table 2, entry 2). The reaction was not so efficient with the heteroaryl dimethyl aluminum reagent **30** derived from 3-pyridine. In such case, the reaction with (*SR*)-**1** led to a poor 20% yield of the corresponding 1,4-addition products **33a** and **33b** as a 60:40 mixture (Table 2, entry 3).

This result obtained from the pyridyl derivative corroborated that the transfer of aryl or heteroaryl groups from the aryl or heteroaryl dimethyl aluminum intermediate to our *p*-quinol **1** only produced good conversions when the aryl group to be transferred is a good nucleophile due to its electron-rich aromatic nature. When the reactivity of the aryl aluminum was high

TABLE 2. Reaction of Heteroaryldimethyl Aluminum 24, 27, and 30 with (*SR*)-*p*-quinol 1



(*SR*)-**1** **31-33a** **31-33b**

entry	[HetArAlMe$_2$]	t (h)	**31-33 (a:b)**	yield (%)
1	 **24**	2	**31a**:**31b** (80:20)	90
2	 **27**	2	**32a**:**32b** (80:20)	75
3	 **30**	4	**33a**:**33b** (60:20)	20

enough, the site selectivity ranged from 95 to 80%, with the pro-*S* double bond always preferred for the conjugate attack on a 4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone having the *R* absolute configuration at the sulfoxide. The π-facial diastereoselectivity of the process was always very high since the conjugate addition occurred exclusively from the face of the 4-hydroxy-2,5-cyclohexadienone system containing the OH group. This must be a consequence of both the smaller size of the OH compared to the CH_2SO*p*-Tol substituent at C-4 and the assistance given by the oxygen in the intermediate of type **C** shown in Scheme 6 in the aryl transfer. This assistance also explains such an easy process with the otherwise poorly reactive aluminum reagents.

Stereoselective Transformations of the Conjugate Adducts. Applications of these site and diastereoselective arylaluminum 1,4-additions with 4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone to asymmetric synthesis of arylcyclitols required the stereoselective transformation of the 1,4-adducts into differently oxygenated systems, as well as the elimination of the β-hydroxy sulfoxide to recover a carbonyl group at C-4. As mentioned above (Scheme 2), the latter had been used by us as a key step in the enantioselective synthesis of different alkyl-substituted polyoxygenated cyclohexane derivatives.[16]

To evaluate the influence of the presence of an aryl group on the stereoselectivity of different transformations en route to the aryl cyclitols, we choose compound (4*R*,5*R*,S*R*)-**2a** as a model. Having in mind our previous protocol, we first oxidized the sulfoxide into sulfone **34** (Scheme 8). Reduction of **34** with DIBAL-H afforded an 80:20 mixture of carbinols **35a** and **35b**, from which **35a** was isolated pure in a 73% yield. The (1*R*,4*R*,6*R*) configuration of **35a** was established on the basis of its NMR parameters and secured by X-ray diffraction.[32] This structural determination also confirmed the configurational assignment of the stereogenic C-4 and C-5 centers of the precursor **2a**, created during the conjugate addition of phenyl dimethylaluminum on *p*-quinol (*SR*)-**1**. The preferred axial attack of small hydrides such as DIBAL-H on rigid cyclohexanones is known to be even higher in cyclohexenones.[33] Considering the structure of **34**, conformation **A** represented in Scheme 8, with the CH_2SO_2*p*-Tol and Ph substituents in pseudoequatorial positions would be more stable than **B**. If **A** is the reactive conformer, the axial attack of the small hydride DIBAL-H explains the major formation of the 1,4-*cis*-diol **35a** in the reduction process. We could improve this stereoselectivity by using $NaBH_4$ in the presence of $CeCl_3$[34] as reduction system. Using MeOH as solvent, we obtained exclusively diastereomer (1*R*,4*R*,6*R*)-**35a** in an almost quantitative yield. With the aim of inverting the stereoselectivity of this reduction, we tried cyclohexenone **34** with L-Selectride, a bulky hydride whose preference for the equatorial approach on rigid cyclohexanone derivatives is well established.[35] Surprisingly, the reaction of compound **34** with L-Selectride gave rise again to an 85:15 mixture of **35a** and **35b**. Although the presence of the pseudoaxial OH at C-4 in conformation **A** of **34** could make the equatorial approach of the hydride by electrostatic interactions difficult,[36] such a preference for the axial attack of the bulky hydride was not expected. Taking into account that the conformational energies of 4-substituted cyclohexene derivatives are smaller than those of the saturated analogues,[37] if we assume that, in this case, **B** is the reactive conformer, the exclusive equatorial approach of L-Selectride would explain the experimental observation. Thus, although in conformer **B** the CH_2SO_2*p*-Tol and Ph groups are in a less favored disposition, the transition state resulting from the equatorial attack of L-Selectride to **B** could be preferred.

In order to recover a carbonyl group at C-1 of **35a** by retroaddition of $MeSO_2$*p*-Tol upon treatment with Cs_2CO_3,[15] we first protected the secondary OH at C-4 as the TBDMS derivative (Scheme 9). Under the reaction conditions previously established by us, after treatment of compound **36** with Cs_2CO_3 in CH_3CN, we observed the formation of $MeSO_2$*p*-Tol **37**, but we were unable to isolate any other product. Fortunately, when we changed the solvent to CH_2Cl_2, the treatment of **36** with Cs_2CO_3, under heterogeneous conditions, allowed the isolation of cyclohexenone (4*R*,6*R*)-**38a** in a 68% yield, together with a 13% yield of the C-6 diastereomer (4*R*,6*S*)-**38b**, formed by epimerization of **38a** under the basic reaction conditions.

Diastereoselective transformations on **38a** were further required to validate our strategy to the phenyl cyclitol derivatives. The *anti* epoxidation of **38a** was achieved in a highly diastereoselective manner using the bulky *tert*-butylhydroperoxide (TBHP) as oxidant and benzyltrimethylammonium hydroxide (triton B, 40% in MeOH)[38] as base. Under these conditions, the epoxide **39** was formed in excellent yield. Reduction of **39** with $NaBH_4$ in the presence of $CeCl_3$[39] afforded an unseparable

(30) Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469–1480, and references cited therein.

(31) Ashby, E. C.; Smith, R. S. *J. Organomet. Chem.* **1982**, *225*, 71–85.

(32) X-ray diffraction of **35a**: CCDC 711956, M_r $C_{20}H_{22}O_4S_1$, unit cell parameters: $a = 9.7463(2)$, $b = 9.6804(2)$, $c = 19.1212(4)$ Å, $\beta = 92.5600(10)°$, space group *P*21; for details, see Supporting Information.

(33) For a review, see: (a) Gung, B. *Tetrahedron* **1996**, *52*, 5263–5301. (b) Wu, Y.-D.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1987**, *109*, 5560–5561.

(34) Li, K.; Hamann, L. G.; Koreda, M. *Tetrahedron Lett.* **1992**, *33*, 6569–6570.

(35) (a) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449–462. (b) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159–7161.

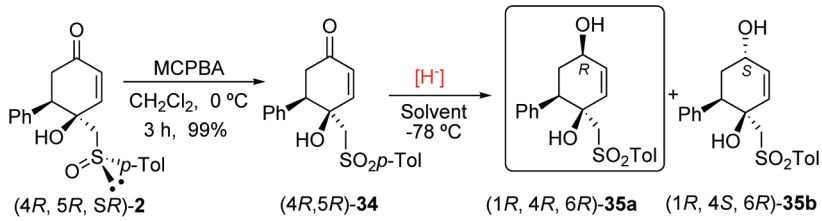
(36) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018–5027.

(37) Conformational energy in cyclic derivatives: difference in free energy between axial and equatorial substituents, see: Eliel, E. L., Wilen, S. H. In *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994.

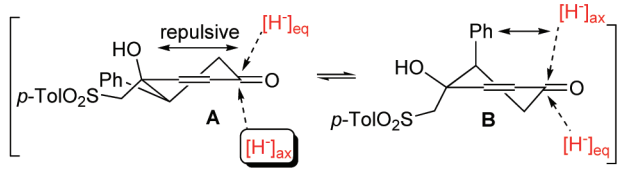
(38) Barros, M. T.; Matias, P. M.; Maycock, Ch. D.; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4321–4323.

(39) Li, K.; Hamann, L. G.; Koreda, M. *Tetrahedron Lett.* **1992**, *33*, 6569–6570.

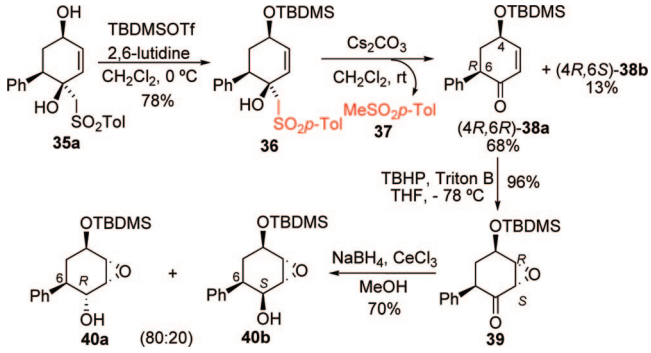
SCHEME 8. Stereoselective Carbonyl Reduction Reaction of 34



[H⁻]	Solvent	35a:35b (Yield)
DIBALH	THF	85 (73%):15 (9%)
$NaBH_4/CeCl_3$	**MeOH**	**100 (99%): 0**
L-Selectride	THF	85:15



SCHEME 9. Synthesis of Polyoxygenated Aryl Cyclitols



mixture of epimeric carbinols **40a** and **40b** in a 80:20 ratio and 70% yield after column chromatography.

In conclusion, we have established a highly stereoselective process to install an aryl substituent at the prochiral 2,5-cyclohexadienone moiety of (*SR*)-4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone **1** using an aryl organoaluminum reagent ($ArAlMe_2$) in the absence of any other catalyst. The aryl or heteroaryl aluminum reagents were generated in situ by treatment of ArLi with $AlMe_2Cl$, and an excess was necessary to achieve the 1,4-addition at the conjugate pro-*S* position in a highly site and π-facial diastereoselective manner directed by both the OH and the sulfoxide. The study carried out allowed us to establish that best yields and selectivities were reached when the aryl nucleophiles bear electron-donating substituents that increase the reactivity of the aluminum reagents. With heteroaryl reagents, the π-excedent nature of the heterocyclic moiety was also essential to give the 1,4-addition products in good yields and stereoselectivities. The method opens an efficient way to create C-aryl stereogenic centers from the prochiral cyclohexadienone moiety. Further transformations of product **2a**, resulting from the reaction of **1** with $PhAlMe_2$, were carried out in order to know the stereoselectivity of reductions and epoxidation reactions, en route to aryl cyclitols. A key step with this aim was the elimination of the β-hydroxy sulfoxide, after oxidation to sulfone, by retroaddition under basic conditions (Cs_2CO_3, CH_2Cl_2), which allowed recovering a carbonyl group. Thus, the β-hydroxy sulfoxide was used to direct the stereoselective aryl conjugate addition and acted as a chiral protecting carbonyl group. The overall process can be regarded as an umpolung since a phenyl group has been introduced α to the ketone using a nucleophilic aryl donor.

Experimental Procedures

(4*R*,5*R*,*SR*)-4-Hydroxy-5-phenyl-4-[(*p*-tolylsulfinyl)methyl]-2-cyclohexenone (2a). To a solution of PhLi (0.96 mL, 1.92 mmol, 2 M in nBu_2O) was added $AlMe_2Cl$ (1.92 mL, 1.92 mmol 1 M in hexane) at 0 °C. The mixture was stirred at room temperature for 30 min and diluted with CH_2Cl_2. A solution of (*SR*)-4-hydroxy-4-[(*p*-tolylsulfinyl)methyl]-2,5-cyclohexadienone **1** (100 mg, 0.38 mmol) in CH_2Cl_2 was then slowly added at 0 °C over the organometallic solution. The reaction mixture was allowed to warm to room temperature. After stirring for 30 min, the reaction was quenched by the addition of saturated aqueous potassium sodium tartrate. The mixture was then extracted with CH_2Cl_2, and the organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude product (96:4 mixtures of diastereomers) was purified by flash chromatography (eluent AcOEt/hexane 3:1). Compounds **2** were obtained as colorless oil in 98% yield as a 96:4 mixture of (4*R*,5*R*,S*R*)-**2a** and (4*S*,5*S*,S*R*)-**2b**: $[\alpha]^{20}_D = +191$ ($c = 0.55$ in $CHCl_3$); ^1H NMR (300 MHz) $\delta = 7.38-7.36$ (AA′, 2H, *p*-Tol), 7.32−7.22 (m, 8H, Ph, H-3 and BB′ system of *p*-Tol), 6.12 (d, $J = 10.2$ Hz, 1H, H-2), 4.27 (s, OH), 3.39 (dd, X part of ABX system, $J = 11.9$ and 3.6 Hz, 1H, H-5), 3.21 (dd, A part of ABX system, $J = 11.9$ and 16.4 Hz, 1H, H-6), 2.89 and 2.70 (AB system, $J = 13.6$ Hz, 2H, CH2*p*-Tol), 2.52 (dd, B part of ABX system, $J = 16.4$ and 3.6 Hz, 1H, H-6), 2.35 (s, 3H); ^{13}C NMR $\delta = 198.8$, 148,6, 142.4, 139.5, 138.1, 130.3 (2C), 129.6 (2C), 129.4, 128.5 (2C), 127.8, 123.9 (2C), 70.7, 64.3, 50.1, 40.4, 21.4; MS (EI) *m/z* (%) 340 (8) $[M]^+$, 324 (98), 306 (19), 236 (100); HRMS calcd for $C_{20}H_{20}O_3S$ 340.1133, found 340.1131 $[M]^+$.

(4*R*,5*R*)-4-Hydroxy-5-phenyl-4-[(*p*-tolylsulfonyl)methyl]-2-cyclohexenone (34). To a solution of **2a** (748 mg, 2.2 mmol, 1.0 equiv) in CH_2Cl_2 (0.5 M) was added dropwise a solution of MCPBA, predried over $MgSO_4$ (475 mg, 2.7 mmol, 1.5 equiv) in CH_2Cl_2. The resulting solution was stirred at 0 °C; once the reaction mixture was completed by TLC, it was hydrolyzed with saturated Na_2SO_3 and extracted with CH_2Cl_2, then the organic layer was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and the solvent was evaporated under reduced pressure to afford compound **34** as a yellowish solid which can be used without further purification (99%, 783 mg): mp 58−60 °C (AcOEt/CH_2Cl_2); $[\alpha]^{20}_D = +4$ ($c = 1.08$, acetone); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 2.36$ (s, 3H, CH_3), 2.47 (dd, part B of the ABX system, $J = 16.6$ and 3.7 Hz, 1H, H_6),

3.12−3.19 (m, 1H, $H_{6'}$), 3.13 and 3.24 (AB system, J = 14.3 Hz, 2H, CH_2), 3.40 (dd, part X of the ABX system, J = 12.4 and 3.7 Hz, 1H, H_5), 3.70 (s, 1H), 6.20 (d, J = 10.3 Hz, 1H, H_2), 7.21−7.22 (m, 7H), 7.42 (d, J = 10.3 Hz, 1H, H_3), 7.62−7.65 (BB′ system, 2H, *p*-Tol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 40.5, 49.8, 62.5, 70.3, 127.6 (2C), 127.9, 128.7 (2C), 129.5, 129.6 (2C), 130.1 (2C), 137.5, 137.9, 145.4, 147.4, 198.5; MS (FAB) *m*/*z* (%) 357 (13) $[M + 1]^+$, 341 (16), 307 (84); HRMS (FAB) calcd for $C_{20}H_{20}O_4S$ 357.1082, found 357.1076 $[M + 1]^+$.

Acknowledgment. We thank MCYT (Grant CTQ2005-02095) and MICINN (Grant CTQ2008-04691) for financial support. M.R. thanks MEC for a Ramón y Cajal contract. E.M. and M.O.G. thank MEC for fellowships, and R.P.A.M. thanks CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) for financial support.

Supporting Information Available: Experimental details and structural data (NMR spectra) for all compounds described within the text and crystallographic data of compounds **5** and **35a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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