Asymmetric Synthesis

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Highly Diastereoselective Synthesis of Orthoquinone Monoketals through λ^3-Iodane-Mediated Oxidative Dearomatization of Phenols**

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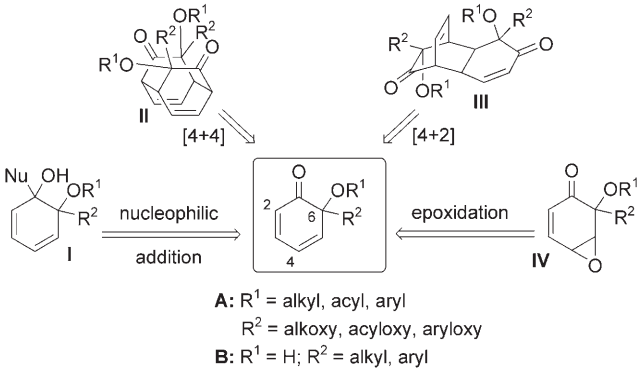
Orthoquinone monoketals **A** and orthoquinols **B** are cyclohexa-2,4-dienone derivatives with valuable reactivity features for the construction of complex molecular architectures.[1] Their conjugated dienone unit and the vicinal positioning of their oxygenated functionalities constitute a unique structural arrangement that can be transformed rapidly into various kinds of polyoxygenated (poly)cyclic systems (Scheme 1).[1]



Scheme 1. Selected synthetically useful transformations of orthoquinone monoketals **A** and orthoquinols **B**.

This chemical versatility has often been demonstrated over the last fifty years, and these benzoquinonoid cyclohexadienones have been used as key intermediates in several syntheses of natural products.[1,2] However, their potential in synthesis has by no means been fully exploited. It still remains to take advantage of their tetrahedral C6 center in asymmetric synthesis. This development has not yet taken place as a result of the lack of efficient methods available for preparing chiral derivatives of **A** and/or **B** in nonracemic form.[1c,3]

Access to these chiral entities would render possible the enantioselective synthesis of many natural products (e.g., calicheamicinone,[2a] trichodimerol,[2b,c] aquaticol,[2d] and scyphostatin[2e] via transformations **I**–**IV**, respectively, Scheme 1), as stated by Pettus and co-workers,[1c] who reported an enantioselective route to paraquinols through diastereoselective phenol dearomatization.[4a] In related concurrent investigations, our initial efforts toward the preparation of orthoquinonoid derivatives relied on the dearomatization of chiral aryl methyl ethers by anodic oxidation.[4b] This approach did furnish orthoquinone monoketals of type **A** as single enantiomers, but only in poor yields, for it required monohydrolysis of bisketal intermediates and could not be applied directly to phenolic substrates. Herein, we report a convenient, high-yielding, and highly diastereoselective route to new monoketals of type **A** through the dearomatization of phenols mediated by hypervalent iodine.

The starting phenols **1** contained a chiral ethanol unit *O*-tethered to the *ortho* position of the phenolic ring (Table 1). These constructs were thus designed to permit their dearomatization into spiroketals of type **A**. A substituent was placed at the *para* position to prevent or at least retard the self-dimerization of the dearomatized species through [4+2] cycloaddition events.[5] The substrates were prepared by a Williamson reaction between 5-substituted 2-benzyloxyphenols and enantiomerically enriched terminal epoxides generated by using the Jacobsen method (see the Supporting Information). After extensive screening of the reaction conditions,[6] we found the use of the λ^3-iodane (diacetoxyiodo)benzene (DIB, 1.0 equiv) in 2,2,2-trifluoroethanol (CF_3CH_2OH, TFE) at −35 °C, followed by quenching of the released acetic acid with powdered $NaHCO_3$ at the same temperature without addition of water, to be optimal in furnishing the desired compounds.

All eight phenolic alcohols **1a**–**h** were converted into the desired spiroketals **2** and **3**, which were isolated in a quantitative combined yield with an excellent level of purity through a simple filtration–evaporation procedure (Table 1). Although the further purification of these products was not necessary before their use in subsequent reactions, they were separated by column chromatography for the characterization of each diastereomer. Their stereochemistry was established unambiguously by NOESY experiments (see the

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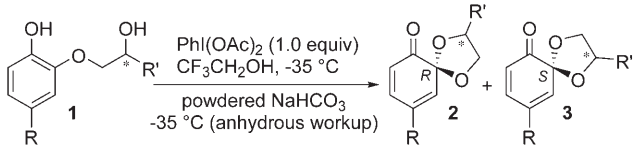
Supporting information for this article, including experimental and theoretical details, and characterization data for all new compounds, is available on the WWW under http://www.angewandte.org or from the author.

Table 1: DIB-mediated spiroketalization of phenolic alcohols **1** into orthoquinone monoketals **2** and **3**.



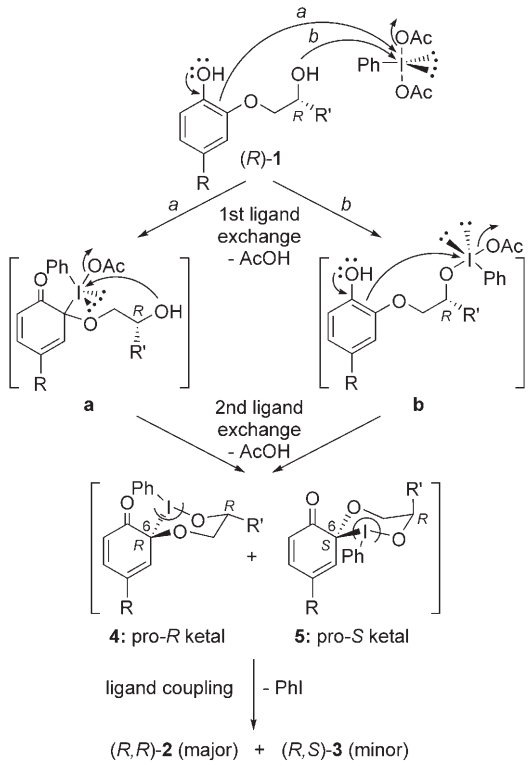
Entry	**1**	R	R′	Products[a]	d.r.[b]
1	(*R*)-**1a**	*t*Bu	*t*Bu	(*R*,*R*)-**2a**/(*R*,*S*)-**3a**	≥95:5
2	(*S*)-**1b**	*t*Bu	*t*Bu	(*S*,*R*)-**2b**/(*S*,*S*)-**3b**	≥5:95
3	(*R*)-**1c**	*t*Bu	Et	(*R*,*R*)-**2c**/(*R*,*S*)-**3c**	60:40
4	(*S*)-**1d**	*t*Bu	Et	(*S*,*R*)-**2d**/(*S*,*S*)-**3d**	40:60
5	(*R*)-**1e**	OMe	*t*Bu	(*R*,*R*)-**2e**/(*R*,*S*)-**3e**	≥95:5
6	(*S*)-**1f**	OMe	*t*Bu	(*S*,*R*)-**2f**/(*S*,*S*)-**3f**	≥5:95
7	(*R*)-**1g**	OMe	$(CH_2)_9CH_3$	(*R*,*R*)-**2g**/(*R*,*S*)-**3g**	60:40
8	(*R*)-**1h**	Br	*t*Bu	(*R*,*R*)-**2h**/(*R*,*S*)-**3h**	≥95:5

[a] The products were isolated in quantitative combined yield. [b] The diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis.

Supporting Information). Phenolic alcohols **1** with a *tert*-butyl substituent on the carbon atom attached to the hydroxy group in the side chain (Table 1, entries 1, 2, 5, 6, and 8) underwent a highly diastereoselective transformation, in contrast to those with an ethyl or *n*-decyl group at this position (Table 1, entries 3, 4, and 7). In all cases, the configuration of the starting alcohol dictated which isomer formed as the major diastereomer: the reactions of enantiomers (*R*)-**1** and (*S*)-**1** furnished (*R*,*R*)-**2** and (*S*,*S*)-**3** as the major product, respectively. These orthoquinone monoketals were isolated as monomers, despite the tendency of such systems to participate in [4+2] cyclodimerization.[5] The only exception to this rule was the unexpected[5b,c] gradual dimerization of **2h** and **3h** (R = Br; Table 1, entry 8) during NMR spectroscopic analysis (see the Supporting Information).

We were satisfied with these results, but intrigued by the mechanism underlying these reactions. On the basis of our recent findings in Ph_2ICl-mediated dearomatizing phenylation,[7a] we hypothesized that these ketalization reactions occur through a ligand-coupling process.[7b–e] This proposal is depicted in Scheme 2 for the *R* series. Thus, a first ligand-exchange step involving nucleophilic attack at the iodine(III) center of DIB by either the delocalized phenol (route *a*) or the side-chain secondary alcohol (route *b*) would displace one of the acetate ligands. The resulting λ^3-iodane derivative **a** or **b** would then undergo a second ligand exchange, this time in an intramolecular fashion. These events would lead to the two key six-membered spiroheterocycles **4** and **5**, the formation of which differs according to the face of the C6 atom at which the connection with the iodine(III) center is made. The evolution of **4** and **5** to products **2** and **3** would then follow through ligand coupling, the driving force of which is the reductive elimination of PhI (Scheme 2).

DFT calculations (B3LYP/6-31G** for C, H, O, and LanL2DZ(d,p) for I; see the Supporting Information) were carried out on **4** and **5** to validate the implication of such iodine(III)-containing ring systems as reaction intermediates. After a meticulous search on the potential energy surface



Scheme 2. Plausible mechanism of the DIB-mediated spiroketalization of phenolic alcohols **1** (*R* series).

(PES), we were rewarded by the localization of both calculated systems **4a**/**5a** (R = R′ = *t*Bu) and **4c**/**5c** (R = *t*Bu, R′ = Et) as local minima (Figure 1). These systems adopt chairlike conformations with a T-shaped iodine(III) center; the pro-*R* intermediate **4** is of higher energy than pro-*S* **5** ($\Delta E = 5.2$ and 4.2 kcal mol^{-1} for **4a**/**5a** and **4c**/**5c**, respectively). We could not locate a transition state; however, as the

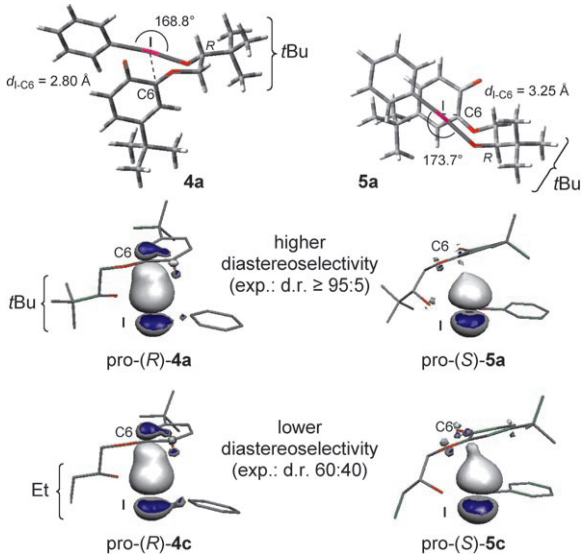
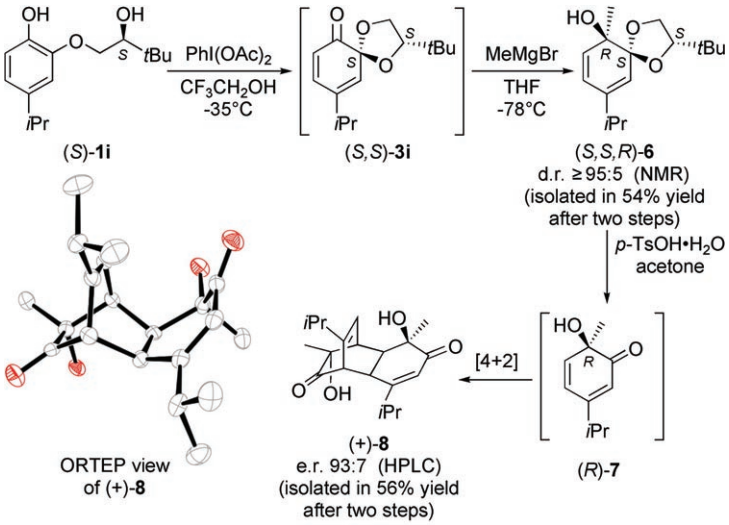


Figure 1. Structures of spiroheterocylic iodine(III) intermediates **4** and **5** calculated by DFT and Molekel plots of the NLMOs associated with the $I^{III} \rightarrow C6$ interaction.

PES appears almost flat around these intermediates before falling abruptly by 50 to 75 kcal mol^{-1} toward the products, this failure to locate a transition state is not very surprising.

These results probably reflect the inherent configurational instability of the geometry of the iodine(III) center, as expressed in Berry-type pseudorotation processes.[7] Such fast ligand permutations involve passage via transient square-pyramidal geometries from which ligand coupling is symmetry allowed.[7c,d] In fact, the calculated T-shaped local minima **4** and **5** most likely precede such tetragonal-pyramidal transition states, which would be reached faster from the higher-energy pro-*R* intermediate **4**. A closer look at the geometrical features of **4** and **5** lent further support to the proposed better predisposition of the pro-*R* system **4** to undergo ligand coupling to give the *R*,*R* product **2** (see Figure 1 and the Supporting Information). For example, the T angle at the iodine(III) center is slightly more bent in pro-*R* **4a** than in pro-*S* **5a** (168.8 versus 173.7°). Most remarkably, both the I–C6 bond length (**4a**: 2.80 Å, **5a**: 3.25 Å) and natural bond orbital (NBO) analysis indicate a much better overlap of the I^{III}- and C6-centered orbitals in pro-*R* **4a**. These differences in orbital overlap are clear in plots created with the Molekel program of the natural localized molecular orbitals (NLMOs) associated with the I^{III}→C6 interaction (Figure 1). The same trends were observed for the **4c**/**5c** system (see the Supporting Information), the NLMOs of which show a smaller overlap difference between pro-*R* **4c** and pro-*S* **5c**, in agreement with the experimentally observed lower diastereoselectivity (Figure 1 and Table 1, entry 3). This pro-*R* preference in the formation of the reaction intermediates was also expressed in the energies of the products. The major product (*R*,*R*)-**2** is more stable than (*R*,*S*)-**3** by 2.9 kcal mol^{-1} for **2a**/**3a** (R′ = *t*Bu) and 1.3 kcal mol^{-1} for **2c**/**3c** (R′ = Et; see the Supporting Information). Thus, all results of the DFT calculations converge to rationalize the diastereoselectivity experimentally observed (Table 1).

The ability of these chiral spiroketals to promote asymmetric induction was demonstrated during the synthesis of (+)-**8** (biscarvacrol),[8a] a naturally occurring type-**III** ring system. For the synthesis of (+)-**8**, we subjected the phenolic alcohol (*S*)-**1i** to our DIB-mediated dearomatization conditions to generate the requisite spiroketal (*S*,*S*)-**3i**, which was treated immediately with MeMgBr to furnish the tertiary alcohol (*S*,*S*,*R*)-**6** with a high level of diastereoselectivity (Scheme 3). The stereochemistry of (*S*,*S*,*R*)-**6** was established unambiguously by a NOESY experiment (see the Supporting Information). The Grignard reagent would attack the ketone from its less-hindered face, the face that is not occupied by the *tert*-butyl group on the spiroketal. This facial differentiation might be amplified by further chelation of the magnesium center with the spiroketal oxygen farther away from the *tert*-butyl group. This two-step sequence illustrates the efficacy of the chiral tether in inducing asymmetry not only during spiroketalization but also during the 1,2-addition of a Grignard reagent. The ketal was then cleaved by treatment with *p*-toluenesulfonic acid. The resulting orthoquinol **7** underwent spontaneous cyclodimerization with complete regioselectivity to afford (+)-**8** as the major stereoisomer (e.r. 93:7; see the Supporting Information).[8b,c] Crystallization from $CHCl_3$ by slow evaporation furnished (+)-**8** as fine white needles, the X-ray analysis of which confirmed unambiguously the structure and absolute configuration of this natural bis(monoterpene).[8a,9]



Scheme 3. Enantioselective synthesis of (+)-biscarvacrol (**8**).

In conclusion, we have developed an efficient route to chiral orthoquinone monoketals in nonracemic form through a λ^3-iodane-mediated dearomatization of phenols. This methodology was applied successfully to the enantioselective synthesis of the bis(monoterpene) biscarvacrol (**8**). Most importantly, this study provides a first but already conclusive rationale for the involvement and stereodifferentiating ability of cyclic iodine(III)-containing intermediates in ligand-coupling reactions.

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[9] CCDC-671171 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

