J. Org. Chem., 72, 7765 (2007)

Synthesis, Optical Resolution, and Configurational Assignment of Novel Axially Chiral Quateraryls[#]

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Abstract— A one-pot, general synthesis of highly functionalized quateraryls through carbanion-induced, base-catalyzed ring transformation of 5,6-diaryl-2*H*-pyran-2-ones and core-substituted phenylacetones is delineated. These conversions were found to give diversely functionalized benzenes bearing peripheral aryl rings, some of which possess inherent atropisomerism. Exemplarily for one of the quateraryls, the optical resolution of the respective atropo-enantiomers by HPLC on a chiral phase and the assignment of their absolute axial configurations succeeded by LC-CD coupling in combination with semiempirical CNDO/S and TDDFT CD calculations. This synthetic approach offers – in a transition metal-free environment – high flexibility in the construction of quateraryls with the desired conformational freedom along the molecular axis, which may help in exploring and developing new potential ligands for asymmetric synthesis.

The demand for new axially chiral, atropisomerically pure biaryls for the use as efficient chiral ligands or auxiliaries in asymmetric synthesis,[1] as chiral phases for chromatography,[2] as important substrates for chiral liquid-crystalline materials,[3] and as reagents for chiral recognition in the field of host-guest chemistry[4] has triggered vigorous efforts to develop

[#] CDRI Communication Number: 7203

new synthetic strategies[5,6,7] to architect novel aromatic scaffolds with the desired degree of conformational flexibility. Nature provides a structurally complex and diverse collection of axially chiral biaryls[8] such as vancomycin,[6] pterocaryanin C,[7] mastigophorenes A and B,[9] gossypol,[10] naphthylisoquinoline alkaloids,[11] and knipholone;[12] their bioactivities often depend on their axial configuration.[13] Moreover, such compounds are fascinating and challenging research objects in material[14] and polymer sciences.[15]

Recently, a great deal of attention has been focused on polyarylated propeller systems that exhibit a geared rotation about a central, planar unit, such as a phenyl ring; these systems can work as molecular rotors and thus have relevance to nanotechnology.[16] Gust et al.[17] and Pepermans et al.[18] investigated rotational isomerism on hexaarylbenzenes with sterically hindered aryl rings and found that the barriers of rotation ($\Delta G^{\ddagger}$) were 38 kcal mol^{-1} and 16 kcal mol^{-1} for the *o*- and *m*-substituted (methyl, methoxy) peripheral aryl rings, respectively. The values were calculated based on the assumption of a one-ring flip mechanism, followed by rotational relaxation of the other five rings. Although correlated rotation in polyarene systems has been extensively investigated either computationally[19] or through solution[20] or solid-state DNMR,[21] less attention has been devoted to study the absolute configuration of atropisomers of such scaffolds.

In this paper, we describe a simple and versatile, one-step pathway to a new type of functionalized quateraryls **3** and, exemplarily for the axially chiral representative **3a**, its enantiomeric resolution on a chiral OD-H phase with online-CD analysis and attribution of the configurationally stable atropo-enantiomers by quantum chemical CD calculations.[22,23]

Although there is great interest in the synthesis of polyarylated scaffolds,[5,6,7,16] methods for their selective and efficient preparation[24] remain sparse. This issue is particularly relevant in the realm of natural product chemistry and in the development of new ligands, where functional-group tolerance is hampered by the lack of general methods. Limited procedures

are known for the synthesis of such biaryls in which one of the aromatic rings is functionalized with two or more aryl substituents in a juxtaposed manner. The palladium-catalyzed aryl-aryl cross-coupling between electrophilic aromatic halides $Ar(X)_n$ (X being generally Br, I, or OTf; n being mainly 0, 1, or 2) and organometallic species Ar-M (M being Mg, Ni, Zn, Sn, or B) is a versatile synthetic method for the preparation of diverse arylated benzenes.[25] Of the various arylation reactions, the Pd-catalyzed Suzuki-Miyaura coupling[26] of a broad array of haloarenes with arylboronic acids is predominant in this area due to the commercial availability and innocuous nature of some of the latter, the easy workup, and the tolerance of aqueous media. However, these coupling reactions normally require elevated temperatures and are susceptible to steric hindrance, which restricts their application in asymmetric biaryl synthesis. Recently, the synthetic potential of such aryl-aryl cross-coupling reactions has been extended to the enantioselective synthesis of axially chiral biaryls,[27] i.e., to the asymmetric version of the Suzuki reaction, of ternaphthyls,[28] and of even more complex scaffolds.[29] Unfortunately, the iterative coupling of tri- or tetrahalides to prepare functionally congested tri- or tetraarylbenzenes *via* selective aryl transfer places constraints on the choice of reagents or catalysts and produces either low yields of the desired compounds or is associated with undesired byproducts.[30]

An alternative non-metal catalyzed approach for the introduction of polyaryl groups onto the benzene skeleton is based on the [4+2] cycloaddition of arylated 2*H*-pyran-2-ones or cyclopentadienones with functionalized alkynes at elevated temperature.[31] Although the versatility of such reactions has been explored in the synthesis of polyphenyl dendrimers[32] and polyphenyl aromatic hydrocarbons,[33] their applicability to the preparation of polyarylbenzenes with restricted rotation around the biaryl axis is limited, due to the difficulties in preparing functionally hindered cyclopentadienones and substituted alkynes. Recently, we reported a highly convenient and generally applicable synthetic route for

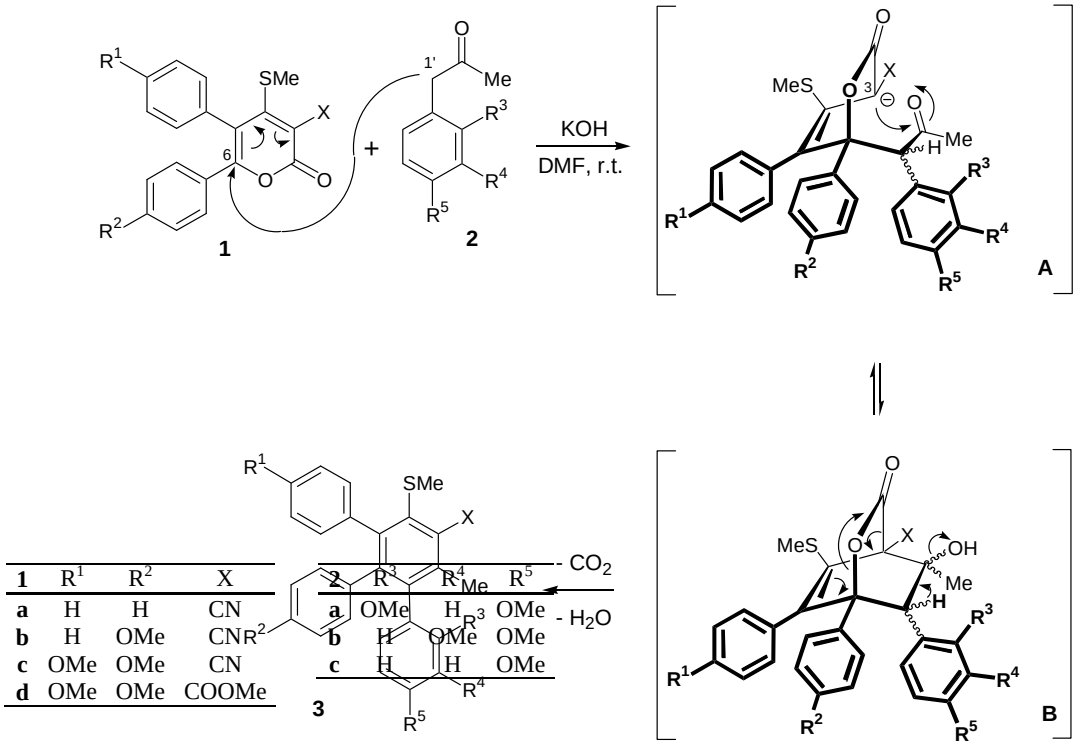
preparing benzenes with di-, tri- or tetraaryl moieties in a controlled fashion in a transition metal-free environment, through simple stitching of α-oxo-ketene-*S,S*-acetals with C-H-activated methylene compounds.[34] In view of an expected specific peripheral aryl ring interaction around the benzene core in the propeller systems and in order to examine their behavior as atropisomers, we have now focused our attention on the preparation and characterization of a new family of axially chiral quateraryls with sterically demanding functionalities.

In the course of our recent studies on the chemistry of 2*H*-pyran-2-ones, we found that 4-methylsulfanyl-2-oxo-6-phenyl-2*H*-pyran-3-carboxylic acid methyl esters are susceptible to Michael additions at position 6 utilizing methylenecarbonyl compounds, leading to the formation of a benzene ring at room temperature.[35] This efficient novel pathway to a benzene ring system under mild basic conditions encouraged us to explore this methodology for preparing various arenes and heteroarenes of particular importance.[36] A characteristic feature of 2*H*-pyran-2-ones **1** is the presence of three electrophilic centers, C2, C4, and C6, which can be used for regioselective reactions with various *C*-, *N*-, and *S*-nucleophiles to generate molecular diversity.

The 5,6-diaryl-2*H*-pyran-2-ones (**1a–d**) used as parent precursors were conveniently prepared by reaction of methyl 2-cyano- or 2-carbomethoxy-3,3-dimethylsulfanyl-acrylate with substituted deoxybenzoins in high yields following Tominaga's protocol.[37] Of the three electrophilic centers, the one at C-6 is highly susceptible to nucleophiles due to the conjugation with even two electron withdrawing substitutents, at C-2 and C-3 of the pyranone ring. Our approach to prepare the functionally hindered quateraryls **3a–g** is based on the ring transformation of the 5,6-diaryl-2*H*-pyran-2-ones **1a–d** using the commercially available substituted phenylacetones **2a–c** as the nucleophilic partner. The synthesis of the 4'-methyl-6'-methylsulfanyl-[1,1';2',1";3',1'"]quateraryl-5'-carbonitriles **3a–f** was achieved by stirring an

equimolar mixture of the 2*H*-pyran-2-ones **1a–d**, the substituted phenylacetones **2a–c**, and powdered KOH in DMF for 12–14 h at room temperature in 59–64% yields (Scheme 1).

SCHEME 1. Synthetic pathway to the functionalized quateraryls 3a–g



1	R^1	R^2	X
a	H	H	CN
b	H	OMe	CN
c	OMe	OMe	CN
d	OMe	OMe	COOMe

2	R^3	R^4	R^5
a	OMe	H	OMe
b	H	OMe	OMe
c	H	H	OMe

3	R^1	R^2	R^3	R^4	R^5	X
a	H	H	OMe	H	OMe	CN
b	H	H	H	OMe	OMe	CN
c	H	OMe	H	H	OMe	CN
d	H	OMe	OMe	H	OMe	CN
e	H	OMe	H	OMe	OMe	CN
f	OMe	OMe	H	OMe	OMe	CN
g	OMe	OMe	OMe	H	OMe	COOMe

The transformation of the 5,6-diaryl-2*H*-pyran-2-ones **1a–c** to the substituted 4'-methyl-6'-methylsulfanyl-[1,1';2',1'';3',1''']quateraryl-5'-carbonitriles **3a–f** is possibly initiated by a 1,5-nucleophilic attack of the carbanion generated by deprotonation of C-1' of the substituted phenylacetones **2a–c** at position C-6 of the respective lactones **1a–c**, with subsequent cyclization by intramolecular nucleophilic attack of the negatively charged C-3 at the carbonyl functionality of **2a–c.** Cycloreversion with elimination of carbon dioxide, followed by dehydration then leads to the substituted 4'-methyl-6'-methylsulfanyl-

[1,1';2',1";3',1"']quaterphenyl-5'-carbonitriles **3a–f** in good yields. In order to check the compatibility of the reaction with the presence of other functional groups, the independent reaction of 5,6-bis-(4-methoxyphenyl)-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carboxylic acid methyl ester (**1d**) with 2',4'-dimethoxyphenylacetone (**2a**) was carried out under the same conditions, affording the quateraryl **3g** in good yield.

In order to investigate the as yet unknown axial chirality of this new class of quateraryls, a method for the resolution of the respective atropo-enantiomers had to be developed, which was exemplarily elaborated for **3a**. In our first experiments, this separation failed with a number of different chiral phases. Only when using a chiral ODH-column (25 × 0.46 cm) at low temperature (5 °C) and a mixture of *n*-hexane/*i*-propanol (99.5:0.5) as the eluent at a constant flow rate of 1 mL min^{-1}, a slight splitting of the HPLC-UV peak of **3a** was achieved. The still poor resolution, however, did not permit measurement of online HPLC-CD curves of suitable quality for the elucidation of the absolute configuration of **3a**. The problem was finally solved by the serial connection of two identical ODH columns, using the same chromatographic conditions as described above, which resulted in the sufficiently separated atropo-enantiomers of **3a** (Figure 1a).

Full LC-CD spectra were recorded in the stopped-flow mode, delivering opposite CD curves for the two peaks, thus confirming the assumption that these peaks indeed represent the two atropo-enantiomers. Due to the novel-type structure of **3a**, an attribution of the absolute configuration to the respective enantiomer was not possible empirically by comparison with the CD behavior of structurally related but configurationally known

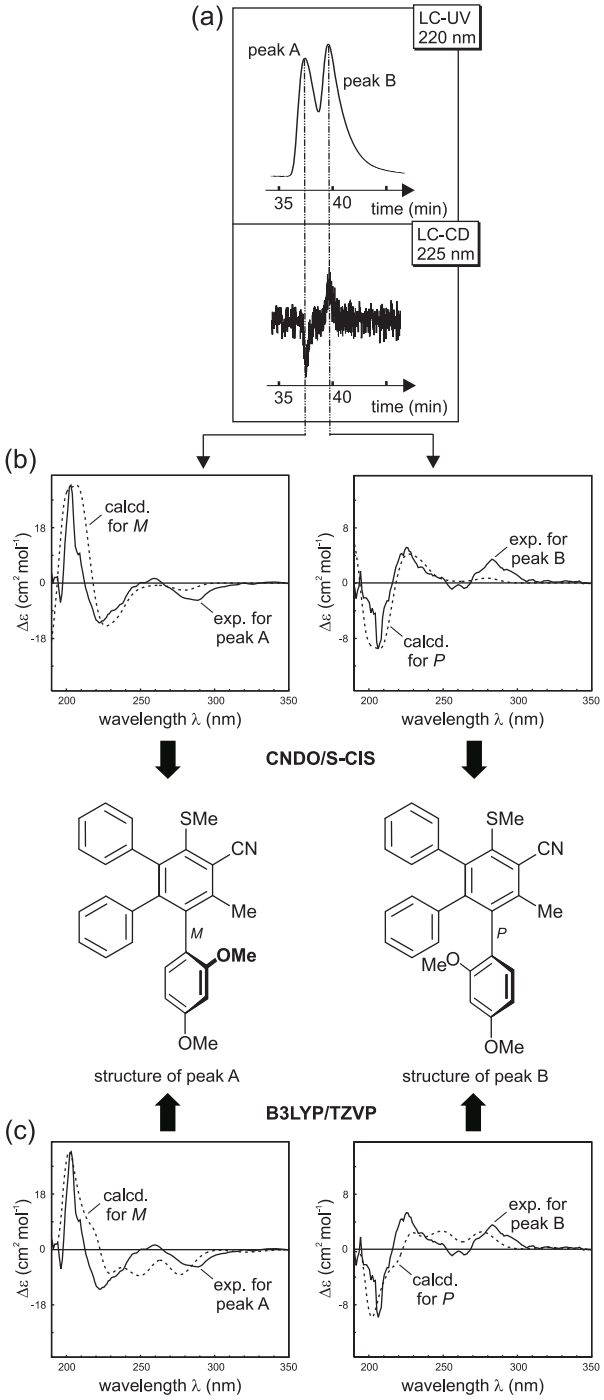


FIGURE 1. Stereochemical assignment of the two atropo-enantiomers of **3a** by (a) LC-CD coupling and quantum chemical CD calculations,[38] applying (b) the semiempirical CNDO/S Hamiltonian and (c) the TDDFT (B3LYP/TZVP) method.

molecules, making the quantum chemical calculation of the CD spectra[22,23] for (*P*)- and (*M*)-**3a** and their comparison with the CD curves measured for the two peaks the method of choice. Arbitrarily starting with (*P*)-**3a**,[38] the conformational space was first investigated by

means of the semiempirical PM3[39] method, resulting in 26 minimum geometries within the energetically relevant range of 3 kcal mol^{-1} above the global minimum.[40] These structures were then submitted to CD calculations, using the CNDO/S[41] Hamiltonian. The single spectra thus obtained were summed up energetically weighted, following the Boltzmann statistics, subsequently UV-corrected,[23] and compared with the experimental CD curves of the two enantiomers. This comparison revealed quite a good agreement between the CD spectrum simulated for (*M*)-**3a** and the experimental one of peak A (Figure 1b, left) and between the curve computed for (*P*)-**3a** and the online spectrum of peak B (Figure 1b, right), thus permitting assignment of the axial *M*-configuration to the faster eluting atropo-enantiomer of **3a** and consequently the *P*-configuration to its more slowly eluting stereoisomer.

Despite the nice agreement obtained with the semiempirical approach (Figure 1b), more sophisticated calculations seemed desirable to confirm the configurational assignment, since the quite complex UV spectrum of **3a** had necessitated a relatively ambiguous and thus uncertain UV correction. Therefore, the 26 minimum structures of (*P*)-**3a** received by means of PM3 were further optimized by using DFT (B3LYP[42]/6-31G*[43]) calculations, thus converging to only six conformers, for which TDDFT (B3LYP/TZVP[44]) computations were carried out. The overall CD spectrum, obtained as described above, did not need to be UV corrected anymore, clearly evidencing the higher quality of the method. The comparison with the two experimental CD curves revealed again a good match between the spectra of (*M*)-**3a** and peak A (Figure 1c, left) on the one hand and between (*P*)-**3a** and peak B (Figure 1c, right) on the other, thus fully confirming the above attribution of the absolute configurations to the two atropo-enantiomers.

In summary, we have demonstrated an efficient and transition metal-free synthetic approach for the synthesis of functionally congested, axially chiral quateraryls through

enolate-induced ring transformation of 5,6-diaryl-2*H*-pyran-2-ones and substituted phenyl acetones in good yields. This synthetic approach offers a high flexibility in the construction of quateraryls with the desired conformational freedom along the molecular axis, which may help in exploring and developing new potential ligands for asymmetric synthesis. The exemplary optical resolution of the quateraryl **3a** by HPLC analysis on a chiral phase and the attribution of the absolute configurations of its atropo-enantiomers by LC-CD coupling in combination with semiempirical CNDO/S and advanced TDDFT CD calculations revealed quite a good agreement between the CD spectrum simulated and the experimental one, thus permitting assignment of the axial *M*-configuration to the faster eluting atropo-enantiomer of **3a** and consequently the *P*-configuration to the more slowly eluting stereoisomer. The work thus demonstrates the methodology for the synthesis and comprehensive stereochemical characterization of such crowded quateraryls in general.

Experimental Section

Detailed synthetic procedures and characterization data for all new compounds are described in the Supporting Information. The data for one of the representative compounds are shown below.

General procedure for the synthesis of 3a–g: A mixture of the respective 5,6-diaryl-4-methylsulfanyl-2*H*-pyran-2-one **1a–d** (1 mmol), the corresponding substituted phenylacetone **2a–c** (1.2 mmol), and powdered KOH (1.2 mmol) in dry DMF (5 mL) was stirred at room temperature for 12–14h. The reaction mixture was poured into ice water with vigorous stirring and then neutralized with dilute aqueous HCl. The solid thus obtained was filtered and purified on a neutral alumina column using chloroform/*n*-hexane (1:4) as the eluent.

2''',4'''-Dimethoxy-4'-methyl-6'-methylsulfanyl-[1,1';2',1'';3',1''']quaterphenyl-5'-carbonitrile (3a). White solid; yield: 62%; R_f 0.49 (60% chloroform in *n*-hexane); mp 204–206 ^{o}C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.35 (s, 3H), 3.63 (s, 3H), 3.72 (s, 3H),

6.26–6.31 (m, 2H), 6.66–7.12 (m, 11H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.7, 55.1, 55.2, 98.0, 104.0, 117.6, 118.6, 120.3, 126.0, 126.4, 126.6, 126.7, 127.2, 127.2, 129.3, 129.9, 130.4, 130.4, 131.3, 138.2, 139.1, 139.2, 142.5, 144.3, 146.8, 157.1, 160.3; IR (KBr) 2221 cm^{-1} (CN); MS (FAB) *m/z* 452 (M^++1); UV/Vis ($CHCl_3$) λ_{max} (ε) = 246 (0.391), 285 (0.188), 327 nm (0.060×10^4 $M^{-1}cm^{-1}$); HRMS calcd for $C_{29}H_{25}NO_2S$: 451.1606, found: 451.1618.

Acknowledgement. This work was supported by the Department of Science and Technology, New Delhi under SERC scheme and by the Fonds der Chemischen Industrie. F.V.S and V.K. are thankful to CSIR, New Delhi, for senior and junior research fellowships.

Supporting Information Available: Complete experimental details and characterization data for the compounds **3a–g** as well as details of the stereochemical and computational analysis of **3a**. This material is available free of charge via the internet at http://pubs.acs.org.

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sulfur and oxygen should not cause a substantial difference of the CD curve of **3a**.

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