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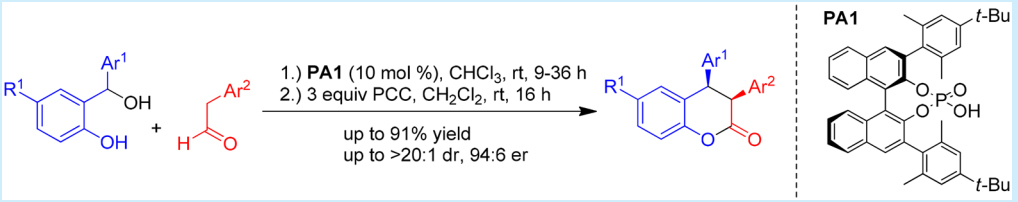
Phosphoric Acid Catalyzed Aldehyde Addition to in Situ Generated *o*-Quinone Methides: An Enantio- and Diastereoselective Entry toward *cis*-3,4-Diaryl Dihydrocoumarins

Matthias Spanka and Christoph Schneider*

Institut für Organische Chemie, Universität Leipzig, Johannisallee 29, 04103 Leipzig, Deutschland

Supporting Information



ABSTRACT: A highly stereoselective, phosphoric acid catalyzed synthesis of *cis*-3,4-diarylchromanols through reaction of *o*-hydroxybenzhydryl alcohols and aryl acetaldehydes is reported. The products can be further manipulated to 3,4-dihydrocoumarins, 4*H*-chromenes, and chromanes with good overall yields and very good diastereo- and enantiocontrol. This reaction is based upon the concept of enol catalysis and comprises the in situ generation of hydrogen-bonded *o*-quinone methides and their formal [4 + 2]-cycloaddition with aldehyde enols.

3,4-Diarylchromans have been widely studied for their potential use against mammary cancer as well as for their estrogenic and antiestrogenic activities (Figure 1). For example, DL-centchroman is an oral nonsteroidal contraceptive sold in India as a selective estrogen receptor modulator (SERM). It has also been intensively studied for the treatment of dysfunctional uterine bleeding (DUB), breast, head, and neck cancer, chronic myeloid leukemia cells, and mastalgia.[1] In addition to centchroman itself, various derivatives thereof have been carefully studied for their activity against osteoporosis and cancer among others.[2]

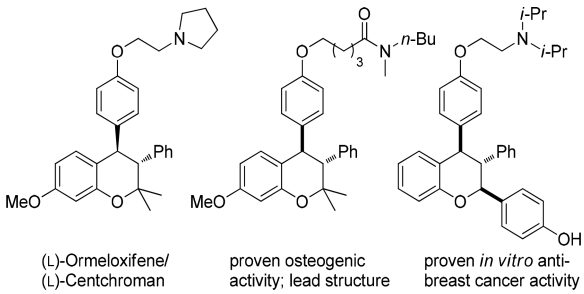


Figure 1. Examples of bioactive compounds containing the 3,4-diarylchroman skeleton.[1,2]

Even though many studies suggest that L-centchroman is far more active than its D-enantiomer or the DL-mixture in many indications, most of the strategies employed to date to synthesize centchroman and derivatives provide them as racemic material or include a resolution step through crystallization.[1] In order to broaden the scope of already existing enantio- and diastereoselective strategies to synthesize chromans,[3] 4*H*-chromenes,[4] and hydrocoumarins,[5] an enantioselective access to all these compound classes by one common intermediate, ideally generated by a chiral catalyst, appears to be highly desirable. We report herein a Brønsted acid catalyzed enantio- and diastereoselective synthesis of *cis*-3,4-diarylchromanols and the corresponding dihydrocoumarins through a formal [4 + 2]-cycloaddition of in situ generated *o*-quinone methides and aryl acetaldehydes. Moreover, the chromanol products **3** were easily converted into a variety of other chroman derivatives by modification of the lactol moiety.

We and others have recently studied in detail the chiral phosphoric acid (CPA) catalyzed addition of π-nucleophiles toward *o*-quinone methides (*o*-QMs), which are generated in situ by dehydration of the corresponding *o*-hydroxy benzhydryl alcohols.[6] A broad range of benzannulated oxygen heterocycles were prepared in excellent yield and enantioselectivity based upon this strategy. In particular, β-dicarbonyl compounds were shown to readily participate in conjugate addition reactions proceeding with exceptional levels of enantioselectivity. As a model to account for the high selectivity, we have proposed a bifunctional activation mode of the phosphoric acid to both the *o*-QM and the enol tautomer of the β-dicarbonyl compound via two hydrogen bonds.

Following this concept ,we envisioned the addition of aryl acetaldehydes **2** as nucleophiles toward *o*-QMs, thereby expanding the scope of these reactions. Given the enol-rich nature of these aldehydes, we expected them to behave as competent nucleophiles being able to form a crucial second

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hydrogen bond to the phosphoric acid by enol catalysis, thereby assembling a highly ordered transition state (Figure 2). In the

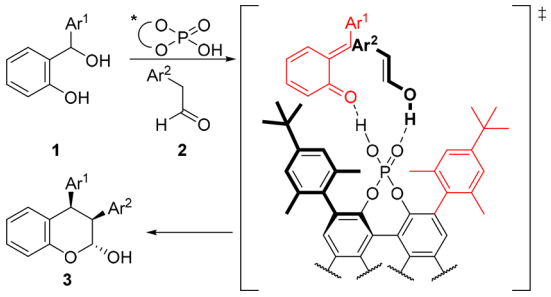
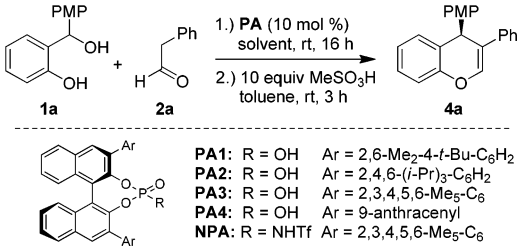


Figure 2. Conceptualization of the reaction and the assumed transition state.

past, hydrogen-bonded enols have been employed as nucleophiles in a number of enantioselective Brønsted acid catalyzed reactions, however, exclusively with ketone-derived enols.[7]

We began our studies with the model reaction shown in Table 1. Benzhydryl alcohol **1a** and phenylacetaldehyde **2a** were

Table 1. Catalyst and Reaction Screening[a]



entry	PA	solvent	time (h)	yield[b] (%)	er[c]
1	**1**	toluene	16	84	79:21
2	**1**	CH_2Cl_2	16	81	84:16
3	**1**	THF	48	no conversion	
4	**1**	**$CHCl_3$**	**16**	**85**	**87:13**
5	**2**	$CHCl_3$	16	66	60:40
6	**3**	$CHCl_3$	16	67	85:15
7	**4**	$CHCl_3$	48	no conversion	
8	**NPA**	$CHCl_3$	16	traces[d]	nd
9	**1**	$CHCl_3$	16	74	86:14[e]
10	**1**	$CHCl_3$	16	71	85:15[f]

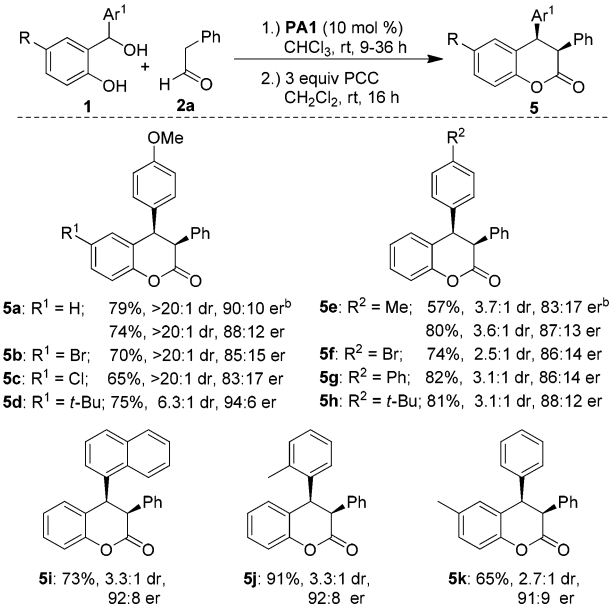
[a]Conditions: catalyst **PA** (0.02 mmol, 0.1 equiv), **1a** (0.20 mmol, 1 equiv), **2a** (0.40 mmol, 2 equiv), and 50 mg of 3 Å MS in 1 mL of solvent. [b]Yield for two-step procedure. [c]Determined by chiral HPLC. [d]Acetal obtained in 46% yield. [e]No 3 Å MS added. [f]Catalyst loading reduced to 5 mol %.

treated with various CPAs (10 mol %)[8] in the presence of molecular sieves at rt. To our delight, the cycloaddition turned out to be the dominant reaction pathway despite some concerns that the starting diol might well undergo an acetalization reaction (product not shown here). In order to simplify the reaction analysis in the initial stages of our investigations, we isolated the product as chromene **4a** after acid-induced dehydration.

Generally good yields of chromene **4a** were isolated with **PA1**−**3** and in various solvents (Table 1). Chlorinated solvents proved to be superior to toluene and THF both in terms of overall yield and enantioselectivity (entries 1−4). Bulky 3,3′-aryl groups within the BINOL backbone were shown to provide the highest enantioselectivity with **PA1** (Ar = 2,6-Me_2-4-*t*-Bu-Ph) being the optimal chiral catalyst (entry 4). Quite interestingly, phosphoric triflylamide **NPA** furnished the product only in trace amounts, while the corresponding acetal was formed as the major product in this reaction (entry 8). Reducing the catalyst loading to 5 mol % or running the reaction without 3 Å MS diminished the yield of the reaction, while the enantioselectivity was almost completely retained (entries 9 and 10).

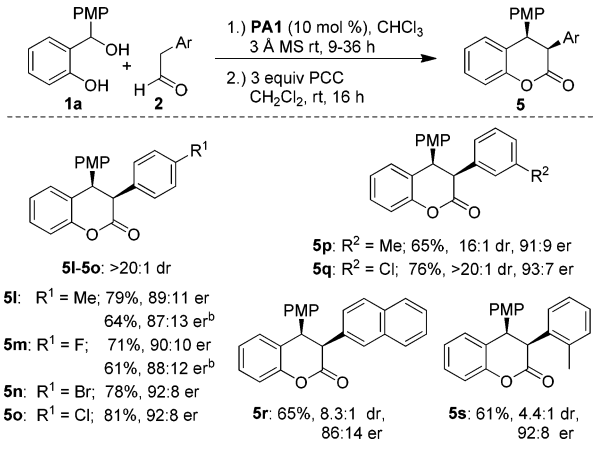
With the optimized reaction conditions (Table 1, entry 4), the substrate scope was next examined (Scheme 1 and 2). For this

Scheme 1. Substrate Scope for the Benzhydryl Alcohol Component 1[a]



[a]Conditions: catalyst **PA1** (0.02 mmol, 0.1 equiv), **1a** (0.20 mmol, 1 equiv), and **2a** (0.40 mmol, 2 equiv) in 1 mL of $CHCl_3$, isolated yield over two steps and for both diastereomers. The er is of the major diastereomer. [b]3 Å MS added.

Scheme 2. Substrate Scope for the Aldehyde Component 2[a]



[a]Conditions: catalyst **PA1** (0.02 mmol, 0.1 equiv), **1a** (0.20 mmol, 1 equiv), **2** (0.40 mmol, 2 equiv), and 50 mg of 3 Å MS in 1 mL of $CHCl_3$, isolated yield over two steps and for both diastereomers. [b]No 3 Å MS added.

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purpose, the initial cycloaddition product, the lactol **3**, was routinely oxidized to the corresponding lactone, the 3,4-dihydrocoumarin **5**, with PCC from which the diastereoselectivity of the reaction could then be determined.

The *β*-aryl substituent of the *o*-QM ends up at the 4-position within the dihydrocoumarin **5**, which could be readily modified in all positions to furnish products with generally good yields and er ranging from 83:17 to 92:8. Better enantioselectivities were observed for sterically more hindered *ortho*-substituted *β*-aryl groups (e.g., **5i** and **5j**), while *para*-substituted aryl groups gave rise to enantioselectivities at the lower end of that range. As an overall trend, we observe that more electron-rich benzhydryl alcohols (e.g., **5a**, **5h**, and **5i**) gave rise to higher degrees of enantioselectivities, especially if the electron-donating group was located on the phenol moiety (compare **5e** and **5k**).

The diastereoselectivity of the reaction was ca. 3−4:1 *cis*/*trans* for most products studied. In that respect, the PMP-substituted coumarins **5a−d** stand out as exceptions as they gave rise to excellent diastereoselectivities of up to >20:1 *cis*/*trans*. To shine some light on this aspect, we studied the formation and diastereoselectivity during the reaction of lactols **3a** and **3b** by online NMR measurements (see the Supporting Information (SI) and Figure 3). Compound **3a** gave rise to a 6:1 *cis*/*trans*

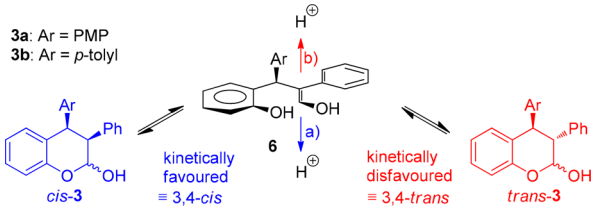


Figure 3. Proposed dynamic equilibrium between the 3,4-*cis* and 3,4-*trans* diastereomers.

ratio after the usual reaction time in the crude reaction mixture, whereas **3b** gave only a 4:1 *cis*/*trans* ratio. More interestingly, the diastereoselectivity proved to be dynamic and changed over time. In addition, it could be increased by SiO_2 column chromatography in the case of **3a**, suggesting an acid-catalyzed epimerization. We assume that the lactol moiety easily opens up and produces a new enol intermediate **6**, which can be protonated on either side. Due to unfavorable steric interactions on the top side by the Ar group, this proton transfer appears kinetically favored on the bottom side of the enol, producing the 3,4-*cis*-diastereomer preferentially (Figure 3).

With **1a** as benzhydryl alcohol, the substrate scope on the aldehyde component was investigated (Scheme 2). Again, generally good yields, excellent *cis*-diastereoselectivity, and up to 93:7 er were obtained across a range of substituted *α*-aryl-substituted acetaldehydes.

Aliphatic aldehydes, lacking the *α*-aryl group, did, however, fail to undergo this transformation, most likely because their enol content was too low for a successful reaction.[9] In addition, 2-phenylpropionaldehyde did not give rise to the corresponding cycloadducts, even though its enol content should be comparable. Most likely, steric hindrance around the *α*-position prevented a successful reaction here. Thus, our investigations document the first example of enantioselective enol catalysis with aldehydes.

We have obtained crystal structures of dihydrocoumarin **5b** and of 4*H*-chromene **4b** which unambiguously reveal both the absolute as well as relative configuration of the products (Figure 4). The sense of asymmetric induction is analogous to our previous studies on a phosphoric acid catalyzed reaction of *o*-QM with enols and enamides, which supports our assumption of a bifunctional activation mode of both *o*-QM and aldehyde enol through the phosphoric acid catalyst.

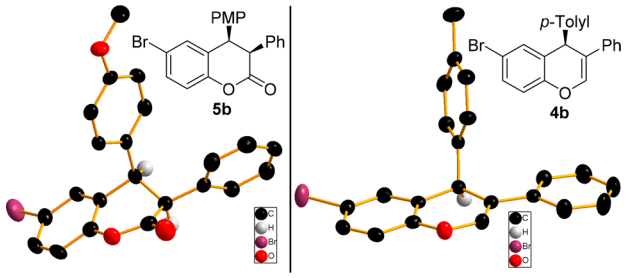
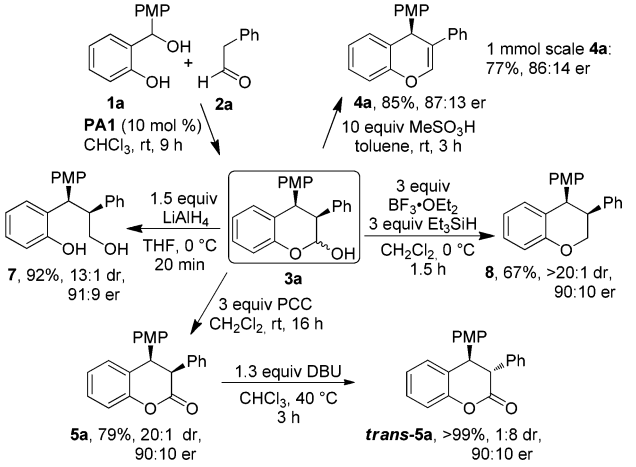


Figure 4. Crystal structure analysis of dihydrocoumarin **5b** and 4*H*-chromene **4b**.

In order to document the versatility of this process, the initially obtained lactol **3a** was transformed into a variety of useful products (Scheme 3). As alluded to before, methanesulfonic acid mediated dehydration delivered 4*H*-chromene **4a** in high yield. Reduction with $LiAlH_4$ produced diol **7**, whereas acid-assisted reduction with $Et_3SiH/BF_3{\cdot}OEt_2$ produced 3,4-diarylchroman **8** in 67% yield. In addition, *cis*-3,4-dihydrocoumarin **5a** was readily epimerized to the thermodynamically more stable 3,4-*trans*-dihydrocoumarin ***trans*-5a** upon treatment with DBU in $CHCl_3$ at 40 °C, which produced a 8:1-*trans*-/*cis*-mixture of **5a**. Accordingly, 3,4-*trans*-dihydrocoumarins are also easily accessible with high enantioselectivity using this strategy.

Scheme 3. Derivatization of Lactol 3a[a]



[a]Conditions: (1) catalyst **PA1** (0.02 mmol, 0.1 equiv), **1a** (0.20 mmol, 1 equiv), **2a** (0.40 mmol, 2 equiv), and 50 mg of 3 Å MS in 1 mL of $CHCl_3$; (2) isolated yield over two steps. For further information, see the SI.

In conclusion, we have developed a new Brønsted acid-catalyzed protocol for a formal [4 + 2]-cycloaddition of in situ generated *o*-QMs and aldehyde enols furnishing 2-chromanols. Upon further oxidation, a broad range of *cis*-3,4-diaryl-3,4-dihydrocoumarins were produced in good yields and with high diastereo- and enantioselectivity. In addition, the initially formed 2-chromanols have been manipulated in numerous ways to access valuable chroman derivatives. In addition, upon

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base-mediated epimerization, the corresponding *trans*-stereoisomers were accessible quantitatively, which should prove important, in particular, for medicinal chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01865.

Detailed experimental procedures, spectral data for all new compounds, and crystallographic data (PDF)

Accession Codes

CCDC 1843089−1843090 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: schneider@chemie.uni-leipzig.de.

ORCID

Christoph Schneider: 0000-0001-7392-9556

Notes

The authors declare no competing financial interest.

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