Asymmetric Catalysis

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Brønsted Acid Catalyzed, Conjugate Addition of β-Dicarbonyls to In Situ Generated *ortho*-Quinone Methides—Enantioselective Synthesis of 4-Aryl-4*H*-Chromenes**

*Osama El-Sepelgy, Stefan Haseloff, Santosh Kumar Alamsetti, and Christoph Schneider**

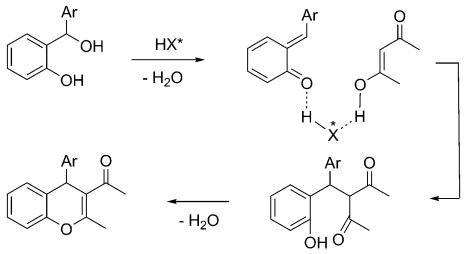
Abstract: *We describe herein a catalytic, enantioselective process for the synthesis of 4H-chromenes which are important structural elements of many natural products and biologically active compounds. A sequence comprising a conjugate addition of β-diketones to in situ generated ortho-quinone methides followed by a cyclodehydration reaction furnished 4-aryl-4H-chromenes in generally excellent yields and high optical purity. A BINOL-based chiral phosphoric acid was employed as a Brønsted acid catalyst which converted ortho-hydroxy benzhydryl alcohols into hydrogen-bonded ortho-quinone methides and effected the carbon–carbon bond-forming event with high enantioselectivity.*

Ortho-Quinone methides are highly reactive intermediates in organic chemistry which have only recently been used synthetically to a greater extent, in particular in the synthesis of chromane systems. They are easily available from a variety of precursors and react as polarized, electron-poor 1-oxabutadienes mostly with electron-rich [2π]-components in hetero-Diels–Alder reactions with inverse electron demand and with nucleophiles in conjugate additions, both with reconstitution of the aromatic π-system.[1]

Catalytic, enantioselective reactions of *ortho*-quinone methides have been reported only rarely.[2] Thus, Sigman and co-workers showed that a chiral palladium–Quinox complex successfully catalyzed the enantioselective dialkoxylation and carboalkoxylation of vinyl phenols and they postulated a palladium *ortho*-quinone methide complex as reactive intermediate.[3] Lectka et al. reported a formal, cinchona alkaloid catalyzed [4+2]-cycloaddition of a stable *ortho*-quinone methide with various silylketene acetals to furnish 3,4-dihydrocoumarins with moderate to good enantioselectivity.[4] Schaus and co-workers employed a chiral 1,1′-binaphthol as catalyst to effect a highly enantioselective addition of aryl and vinyl boronates to in situ generated *ortho*-quinone methides proceeding under very mild conditions.[5] Most recently, the groups of Ye and Scheidt independently reported N-heterocyclic carbene catalyzed enantioselective [4+3]-cycloadditions of α,β-unsaturated aldehydes and *ortho*-quinone methides in the synthesis of benzoxopinones.[6]

The chromane skeleton belongs to the privileged structural motifs in the field of natural products as well as in the area of pharmaceutically active compounds which exhibit cytotoxic, antibacterial, antiviral, antiinflammatory, and antioxidant activities.[7] Previous synthetic strategies specifically towards the synthesis of 4*H*-chromenes furnished racemic products in most cases.[8] Only in the last years a few enantioselective processes have been developed which are, however, limited to very special substrates.[9] Only the palladium-catalyzed, enantioselective, conjugate addition of aryl boronic acids to enones developed by Miyaura and coworkers gave rise to some pharmacologically valuable 4-aryl-4*H*-chromenes with high optical purity.[9a]

We report herein the first Brønsted acid catalyzed, conjugate addition of β-dicarbonyls to in situ generated *ortho*-quinone methides, which proceed with good to excellent enantioselectivity and through a subsequent cyclodehydration reaction furnish optically highly enriched 4-aryl-4*H*-chromenes with a broad substitution pattern (Scheme 1). As substrates for the in situ formation of the *ortho*-quinone methides we have employed *ortho*-hydroxy benzhydryl alcohols which had previously been employed in Lewis acid catalyzed syntheses of racemic 4*H*-chromenes.[8h–j] We reasoned that a chiral Brønsted acid would not only generate the catalyst-bound *ortho*-quinone methide, but at the same time also remain attached to the enol tautomer of the β-dicarbonyl compound through hydrogen bonding such that an enantioselective reaction would occur via a highly ordered transition state.[10]



Scheme 1. Conceptualization of the synthesis of 4-aryl-4*H*-chromenes.

[*] M. Sc. O. El-Sepelgy, M. Sc. S. Haseloff, Dr. S. K. Alamsetti, Prof. Dr. C. Schneider
Institut für Organische Chemie, Universität Leipzig
Johannisallee 29, 04103 Leipzig (Germany)
E-mail: schneider@chemie.uni-leipzig.de
M. Sc. O. El-Sepelgy
Permanent Address: Faculty of Chemistry
Jagiellonian University Krakow
Ingardena 3, 30060 Krakow (Poland)

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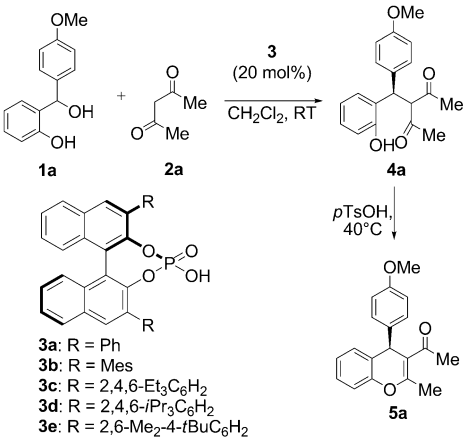
Our studies are conceptually related to the work of Rueping[11] and Bach[12] in which secondary *ortho*-hydroxybenzylic alcohols were employed under similar conditions as substrates for enantioselective allylic alkylation reactions and for the addition of indole nucleophiles, respectively.[13]

We started our investigations with the reaction of *ortho*-hydroxy benzhydryl alcohol **1a** (1 equiv) and acetylacetone (**2a**; 3 equiv) in CH_2Cl_2 in the presence of various chiral, BINOL-based phosphoric acids **3** (20 mol%; Table 1). The addition product **4a** was obtained in good yields within 24 h at room temperature and was subsequently cyclodehydrated to give the desired 4*H*-chromene **5a** through addition of *para*-toluenesulfonic acid (20 mol%) at 40°C. Control experiments revealed that the optical purity of **4a** and **5a** was identical in each case. Whereas the 3,3′-diphenyl-substituted BINOL phosphoric acid **3a** gave rise to low enantioselectivity in this reaction (entry 1), higher selectivity was observed with sterically more demanding 3,3′-aryl substituents in the BINOL backbone of the Brønsted acid catalyst. The highest selectivity was eventually obtained with phosphoric acid **3e** (Ar = 2,6-Me_2-4-*t*BuC_6H_2) which delivered the addition product **4a** with 97% yield and 85:15 e.r. (entry 5). In toluene and $CHCl_3$ as solvent this selectivity was further enhanced to 86:14 e.r. and 89:11 e.r., respectively, while maintaining excellent yields (entries 6 and 7). The catalyst loading could be lowered to only 5 mol% and the amount of diketone was reduced to 1.2 equiv as well without compromising yield or selectivity of this reaction. When this conditions were applied 4*H*-chromene **5a** was isolated in 82% overall yield and 88:12 e.r. (entry 8).

Additional *ortho*-hydroxy benzhydryl alcohols **1** were submitted to the reaction with acetylacetone (**2a**) under these optimized conditions and converted into the corresponding 4-aryl-4*H*-chromenes **5a–d** in good yields and high optical purity (Figure 1).

Table 1: Optimization of the phosphoric acid catalyzed addition of acetylacetone (2a) to *ortho*-quinone methides generated in situ.[a]



Entry	Product	Catalyst	Yield [%]	e.r.[e]
1	**4a**	**3a**	70	56:44
2	**4a**	**3b**	95	78:22
3	**4a**	**3c**	97	84:16
4	**4a**	**3d**	97	81:19
5	**4a**	**3e**	97	85:15
6[b]	**4a**	**3e**	88	86:14
7[c]	**4a**	**3e**	95	89:11
8[c,d]	**5a**	**3e**	82	88:12

[a] Reaction conditions: 0.20 mmol (1.0 equiv) *ortho*-hydroxy benzhydrylic alcohol **1**, 0.60 mmol (3.0 equiv) acetylacetone (**2a**), catalyst **3** (20 mol%), 1 mL CH_2Cl_2, RT, 24 h. [b] Solvent 1 mL toluene. [c] Solvent 1 mL $CHCl_3$ [d] 0.24 mmol (1.2 equiv) acetylacetone (**2a**), catalyst **3** (5 mol%). [e] Determined by HPLC on a chiral stationary phase (see the Supporting Information).

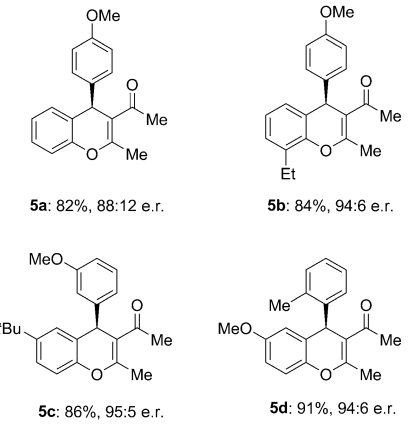
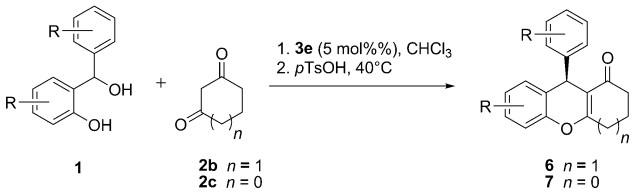


Figure 1. Phosphoric acid catalyzed, enantioselective synthesis of 4-aryl-4*H*-chromenes **5** (reaction conditions see Table 1, entry 8).

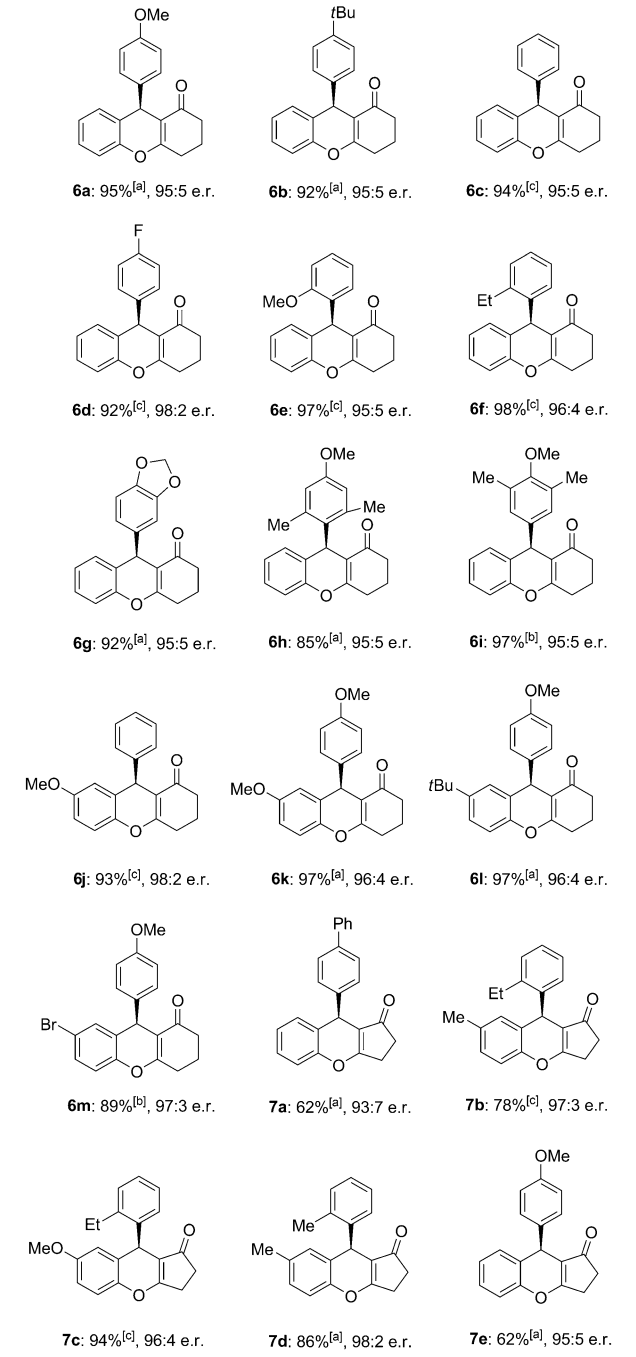
This process could easily be extended to other β-diketones as well. In particular, cyclic diketones turned out to be excellent substrates. Thus, 1,3-cyclohexanedione (**2b**) was converted into tetrahydroxanthenone **6a** in 95% overall yield and with 95:5 e.r. (Scheme 2). Reaction of **2b** with other aryl-substituted *ortho*-quinone methides furnished products **6b–i** in excellent overall yields and with high enantioselectivity of at least 95:5 e.r. It is noteworthy that *ortho*-substituted and even *ortho*-disubstituted aryl substituents within the *ortho*-quinone methide were readily tolerated and delivered xanthenones **6e**,**f** and **6h** with excellent yield and selectivity. A substitution within the quinone methide fragment was possible as well and the corresponding xanthenones **6j–m** were obtained in almost quantitative yields and up to 98:2 e.r. Moreover, the bromo-substituted xanthenone **6m** gave crystals suitable for X-ray crystallography which proved the absolute configuration of the reaction products (Figure 2).[14]

Reactions with 1,3-cyclopentanedione (**2c**) went equally well and delivered cyclopenta[*b*]benzopyranones **7a–e** directly with high enantioselectivity of up to 97:3 e.r. The addition of *para*-toluenesulfonic acid to effect the subsequent dehydrative cyclization was not necessary here as the intermediate conjugate addition product cyclized directly to give the final benzopyranone **7**. Again, *ortho*-aryl-substituted quinone methides underwent particularly enantioselective reactions (**7b–d**).

Through simple structural modification within the diketone component the corresponding oxa- and thiaxanthenones



1 | 2b n = 1, 2c n = 0 | 6 n = 1, 7 n = 0



Scheme 2. Phosphoric acid catalyzed, enantioselective synthesis of 9-aryl-1*H*-xanthen-1-ones **6** and cyclopenta[*b*]benzopyranones **7**. Reaction conditions: 0.20 mmol (1.0 equiv) *ortho*-hydroxy benzhydryl alcohol **1**, 0.24 mmol (1.2 equiv) 1,3-cycloalkanedione **2b**/**2c**, catalyst **3e** (5 mol%), 1 mL $CHCl_3$, 24 h. Reaction temperature: [a] 0°C, [b] 10°C, [c] RT. Reactions with 1,3-cyclopentanedione (**2c**) delivered cyclopenta-[*b*]benzopyranone **7** directly without the addition of *p*TsOH. e.r. values were determined through HPLC on a chiral stationary phase (see the Supporting Information).

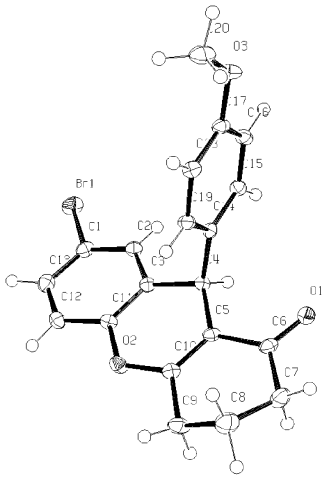
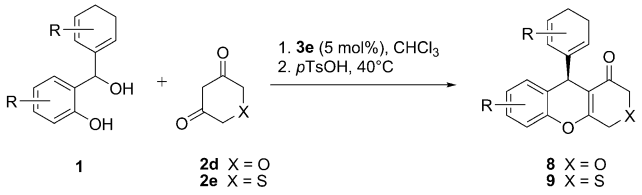
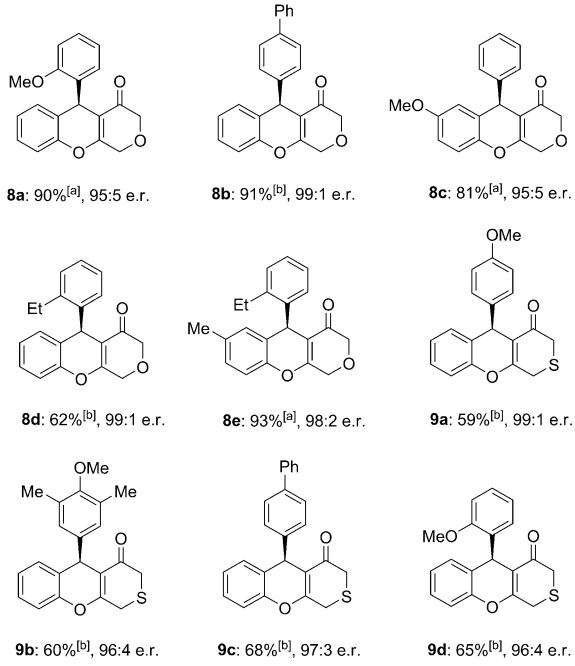


Figure 2. Crystal structure of the bromo-substituted xanthenone **6m**. Thermal ellipsoids at 50% probability.

were easily accessible as well (Scheme 3). Thus, 3,5-pyranedione (**2d**) reacted with various *ortho*-hydroxy benzhydryl alcohols **1** under the optimized reaction conditions to furnish



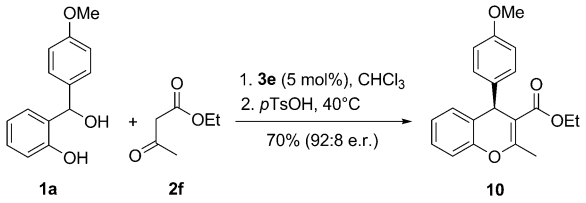
1 | 2d X = O, 2e X = S | 8 X = O, 9 X = S



Scheme 3. Phosphoric acid catalyzed, enantioselective synthesis of heterosubstituted xanthenones **8**/**9**. Reaction conditions see Scheme 2. Reaction temperature: [a] 0°C, [b] RT. Reactions with 3,5-pyranedione (**2d**) delivered 3-oxaxanthenons **8a**–**e** directly without the addition of *p*TsOH. e.r. values were determined by HPLC on a chiral stationary phase (see the Supporting Information).

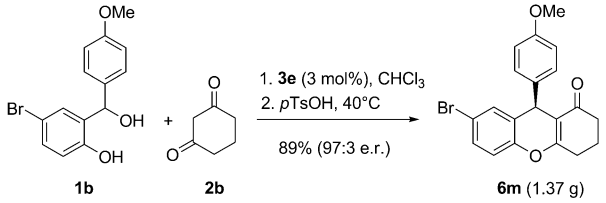
3-oxaxanthenones **8a–e**; likewise 3,5-thiapyrandione (**2e**) gave rise to the corresponding 3-thiaxanthenones **9a–e** by means of this annulation process. Both reactions proceeded in typically good yields and excellent enantioselectivities as well.

The entire process was readily extended to reactions with β-ketoesters as substrates. Thus, ethyl acetoacetate (**2f**) and *ortho*-hydroxy benzhydryl alcohol **1a** reacted under standard conditions to furnish 4-*para*-methoxyphenyl-4*H*-chromene **10** in 70% yield and with 92:8 e.r. (Scheme 4).



Scheme 4. Phosphoric acid catalyzed reaction with ethyl acetoacetate (**2f**).

In order to demonstrate the practicality of this process we conducted the synthesis of xanthenone **6m** on a gram-scale. With only 3 mol% of Brønsted acid catalyst **3e** the conjugate addition reaction proceeded to completion within 24 h at room temperature and after subsequent acid-catalyzed cyclodehydration 1.37 g (89%) of product **6m** was obtained with 97:3 e.r. which was further enhanced to >99:1 e.r. through recrystallization (Scheme 5).



Scheme 5. Synthesis of xanthenone **6m** on a gram scale.

We assume that the chiral phosphoric acid is attached to both the *ortho*-quinone methide and the enol tautomer of the β-diketone through hydrogen bonds and guides both components in a highly ordered transition state. On the basis of the absolute configuration of the products secured through the crystal structure analysis we propose a transition structure similar to the one depicted in Figure 3. The 3-aryl group within the BINOL backbone of the catalyst (Ar^2), which is positioned in close proximity to where the reaction occurs, effectively shields the upper side of the *ortho*-quinone methide and directs the incoming enol nucleophile to its lower side.

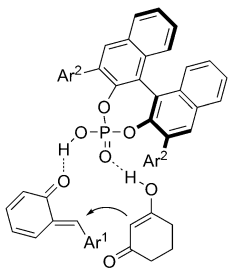


Figure 3. Proposed transition structure of the reaction.

In conclusion, we have developed a broadly applicable, phosphoric acid catalyzed, enantioselective, conjugate addition of β-dicarbonyl compounds to in situ generated *ortho*-quinone methides and subsequently converted the addition products into synthetically valuable 4-aryl-4*H*-chromenes and related heterocycles through a cyclodehydration reaction. Products were obtained in typically excellent yields and high optical purity, and the practicality of the process was documented in a large-scale experiment in which only 3 mol% of the Brønsted acid catalyst was required for identical results. This study significantly broadens the scope of chiral phosphoric acid catalysis and we expect that other nucleophiles may be submitted to reactions with hydrogen-bonded *ortho*-quinone methides according to this scheme as well. The detailed investigation of the reaction described herein and extension of this methodology are currently in progress in our laboratories.

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Keywords: asymmetric synthesis · benzhydrylic alcohols · chiral phosphoric acids · chromenes · xanthenones

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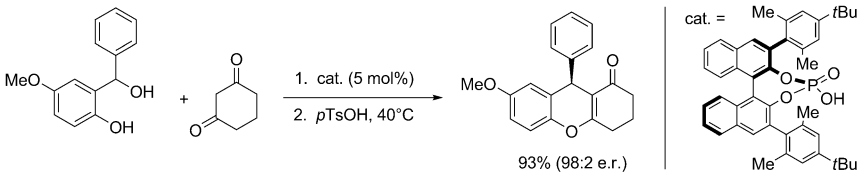
[14] CCDC 969295 (**6m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. For details concerning the crystal structure of **6m** see the Supporting Information as well.

Communications

Asymmetric Catalysis

O. El-Sepelgy, S. Haseloff, S. K. Alamsetti, C. Schneider* ——— ■■■■–■■■■

Brønsted Acid Catalyzed, Conjugate Addition of β-Dicarbonyls to In Situ Generated *ortho*-Quinone Methides—Enantioselective Synthesis of 4-Aryl-4*H*-Chromenes



Chiral phosphoric acids permit the in situ generation of hydrogen-bonded *ortho*-quinone methides which react with β-diketones and β-keto esters with excellent enantioselectivity and furnish valuable 4-aryl-4*H*-chromenes and related heterocycles upon subsequent cyclodehydration. These observations extend the substrate scope of enantioselective phosphoric acid catalysis towards an important additional class of compounds.