

Enantio- and Diastereoselective Access to Distant Stereocenters Embedded within Tetrahydroxanthenes: Utilizing *ortho*-Quinone Methides as Reactive Intermediates in Asymmetric Brønsted Acid Catalysis**

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Abstract: A protocol for the highly enantioselective synthesis of 9-substituted tetrahydroxanthenones by means of asymmetric Brønsted acid catalysis has been developed. A chiral binol-based *N*-triflylphosphoramidate was found to promote the *in situ* generation of *ortho*-quinone methides and their subsequent reaction with 1,3-cyclohexanedione to provide the desired products with excellent enantioselectivities. In addition, a highly enantio- and diastereoselective Brønsted acid catalyzed desymmetrization of 5-monosubstituted 1,3-dicarbonyl substrates with *ortho*-quinone methides gives rise to valuable tetrahydroxanthenes containing two distant stereocenters.

The development of simplified and atom-economic strategies for rapid access to complex enantiomerically enriched structural motifs featured in natural products is one of the main tasks in synthetic chemistry.^[1] For example, 4*H*-chromene is an intriguing core structure which is present in many fascinating natural products having remarkable biological and pharmacological properties.^[2] While procedures for the synthesis of chiral chromenes have been reported,^[3] the direct asymmetric synthesis of more complex and representative target scaffolds, such as tetrahydroxanthenes embedding one or two stereocenters (Figure 1), has not been described.

ortho-Quinone methides (*o*-QMs) were introduced by Fries,^[4] and are widely exploited as useful synthetic intermediates for the construction of complex natural products and bioactive compounds.^[5,6] *o*-QMs can be obtained by a variety of methods^[7] including oxidation,^[7a] thermolysis,^[7b] photolysis,^[7c] transition-metal catalysis,^[8] and base-^[7d] and acid-mediated transformations.^[7e] *o*-QMs have been mainly applied in Michael addition reactions, 6*π* electrocyclizations or [4+2] cycloadditions, and often lead to the synthesis of chromane and chromene skeletons.^[9] Given the inherently transient nature of *o*-QMs, a feature resulting from their tendency of rearomatization or dimerization, the generation of enantiomerically enriched products still remains a great challenge.^[9–12]

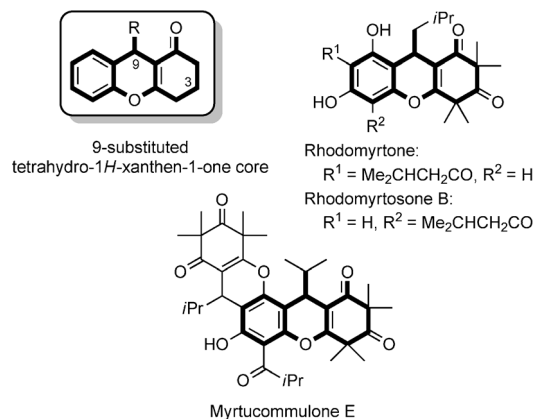
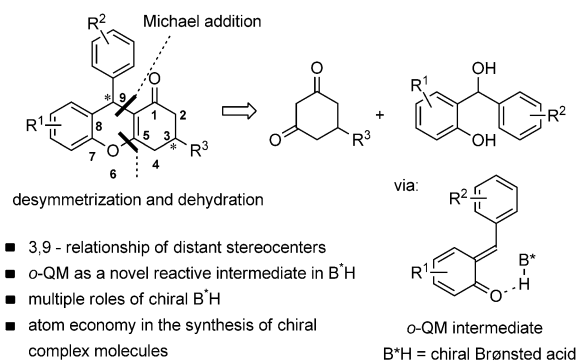


Figure 1. Natural products with 9-substituted tetrahydro-1*H*-xanthen-1-one core.

Thus we decided to develop a new asymmetric Brønsted acid catalyzed process for a fast and streamlined synthesis of valuable tetrahydroxanthenes by using *o*-QMs as reactive intermediates.

Despite the flourishing advancement of asymmetric Brønsted acid catalysis over the past decade,^[13,14] the majority of the developed transformations involve species which have good coordination ability to the catalyst, for example, imines, carbonyl groups, and oxocarbenium ions. Inspired by DFT computational studies described by Freccero in 2001,^[15] who reported that hydrogen bonding by water or acid catalysis can enhance the reactivity of *o*-QMs, we questioned whether asymmetric Brønsted acid catalysis could be extended to reactions involving *o*-QMs (Scheme 1). Typically, Brønsted



Scheme 1. *o*-QMs as reactive intermediates in Brønsted acid catalyzed asymmetric synthesis.

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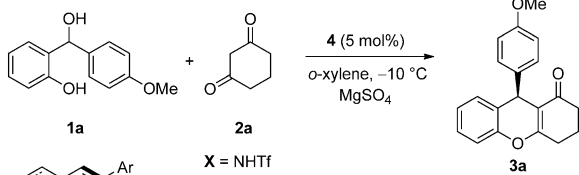
acid promoted enantioselective reactions including desymmetrizations^[16] establish stereocenters in close proximity (e.g., 1,2- or 1,3-relationship). To the best of our knowledge, the establishment of more distant stereocenters using this catalytic mode has never been reported. Often, compounds which bear two remote stereocenters are obtained from pre-established chiral precursors under remote asymmetric induction.^[17,18]

Herein, we document a new catalytic asymmetric desymmetrization of *meso*-1,3-dicarbonyl compounds with in situ generated *o*-QMs to provide a distant relationship of two stereocenters in tetrahydroanthene derivatives (3- and 9-positions) with excellent diastereomeric ratio and enantiomeric excess. Furthermore, the highly enantioselective synthesis of tetrahydroanthenes bearing a chiral center in the 9-position is also described. To avoid limitations in substrate scope resulting from the difficulty of isolating *o*-QMs, we decided to use hydroxybenzyl alcohol derivatives as precursors for *o*-QMs. These have been used in the photolytic and thermal in situ generation of *o*-QMs with the advantage of being readily prepared in one step from commercially available salicylaldehydes and arylmagnesium bromide. Guided by our previous research interest in cascade transformations we chose **2a** (see Table 1) as a nucleophile for initial investigations.

Thus, we began our studies by examining the Brønsted acid catalyzed reaction of the hydroxybenzyl alcohol **1a** with 1,3-diketone **2a** as model substrates. Initially, an array of chiral *N*-triflylphosphoramides (NTPAs)^[14] (**4a–i**) was evaluated (Table 1, entries 1–9) with the 3,3'-bis(2-naphthyl)-substituted NTPA **4h** providing good results for both enantioselectivity and yield (entry 8). Further optimization was carried out by employing different solvents. Use of *o*-xylene resulted in a slightly better enantioselectivity (entry 12). With MgSO₄ as an additive, a slight increase in both yield and selectivity was observed (entry 13), and lowering the temperature to –10 °C provided higher enantiomeric excess without affecting the yield (entry 14). A control experiment without catalyst revealed that the NTPA is essential for the reaction to occur (entry 16).

Then we turned our attention to explore the generality of the Brønsted acid catalyzed addition/cyclization cascade reaction of *o*-QMs and dicarbonyl analogues. In general, cycloadducts with high enantiomeric excesses are obtained in good yields regardless of their electronic properties (Table 2). Firstly, a wide variety of *p*-methoxy-substituted hydroxybenzyl alcohols with nonsubstituted (**1a**), electron-donating (**1b**, **1c**), and electron-withdrawing (**1d**) substituents were tested and all substrates participated smoothly in this cascade reaction, thus furnishing the corresponding cycloadducts **3a–d** with good yields (68–79 %) and excellent enantioselectivities (93–98 % *ee*). 1-Naphthalene hydroxybenzyl alcohol (**1e**), a more sterically demanding substrate, furnished the product **3e** with a slightly diminished yield and good enantiomeric excess. Next, substrates with an *O*-allyl group in the *para*-position have been tested. Various hydroxybenzyl alcohols (**1f–j**) bearing either an electron-withdrawing or electron-donating group in different positions of the quinone methide fragment, all functioned efficiently. We then con-

Table 1: Optimization of the Brønsted acid catalyzed addition with in situ generated *o*-QM.



1a + **2a** $\xrightarrow[4 \text{ (5 mol\%)}]{\text{o-xylene, } -10^\circ\text{C, MgSO}_4}$ **3a**

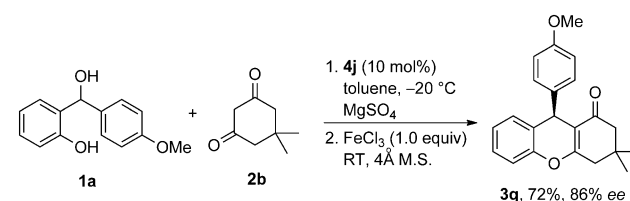
X = NHTf
4a: Ar = C₆H₅
4b: Ar = 4-biphenyl
4c: Ar = 3,5-(CF₃)₂C₆H₃
4d: Ar = 9-phenanthryl
4e: Ar = 2,4,6-*i*-Pr₃C₆H₂
4f: Ar = [H₈]-1-naphthyl
4g: Ar = 1-naphthyl
4h: Ar = 2-naphthyl
4i: Ar = [H₈]-2-naphthyl
X = OH
4j: Ar = 2,4,6-*i*-Pr₃C₆H₂

Entry ^[a]	Solvent	T [°C]	4	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	toluene	0	4a	64	57
2	toluene	0	4b	66	77
3	toluene	0	4c	56	0
4	toluene	0	4d	67	83
5	toluene	0	4e	71	89
6	toluene	0	4f	70	89
7	toluene	0	4g	68	85
8	toluene	0	4h	73	91
9	toluene	0	4i	69	86
10	CH ₂ Cl ₂	0	4h	85	43
11	<i>m</i> -xylene	0	4h	71	85
12	<i>o</i> -xylene	0	4h	73	93
13 ^[d]	<i>o</i> -xylene	0	4h	74	94
14 ^[d]	<i>o</i> -xylene	–10	4h	71	98
15 ^[d,e]	<i>o</i> -xylene	–10	4h	62	90
16 ^[f]	<i>o</i> -xylene	–10	–	–	–

[a] Reactions were performed with the alcohol **1a** (0.07 M concentration), cyclohexane-1,3-dione **2a** (3 equiv), and 5 mol % **4**. The solution was stirred at the indicated temperature for 8 h, and then at RT for another 8 h. [b] Yield of isolated product after column chromatography.

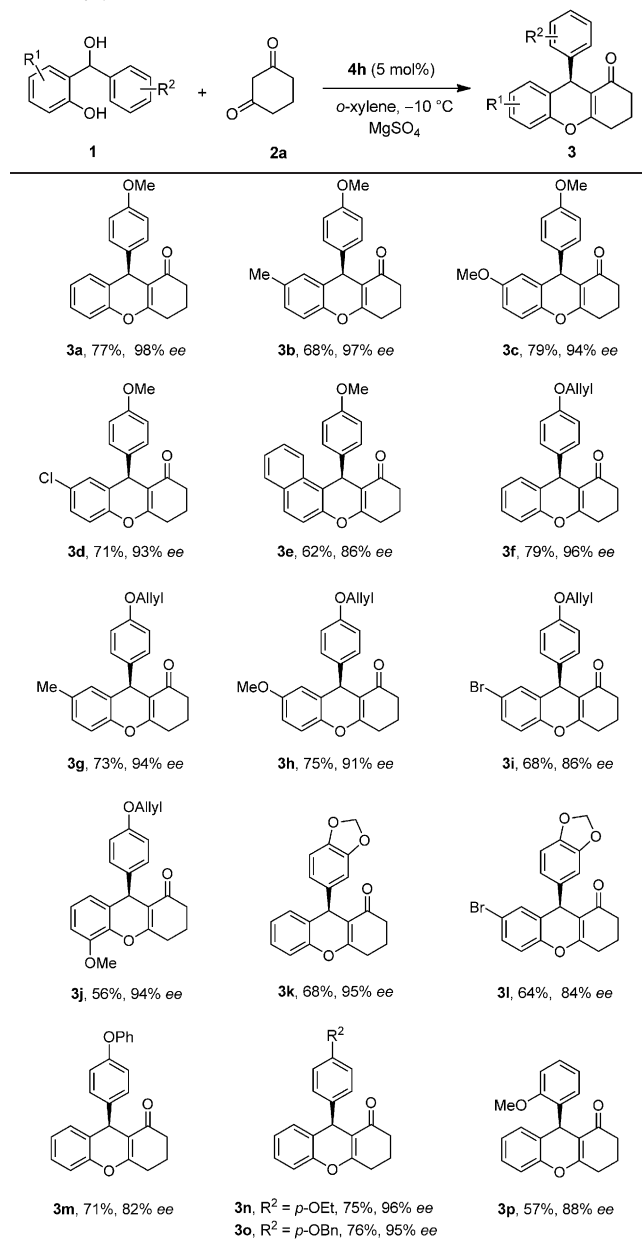
[c] Enantiomeric excess was determined by HPLC on chiral stationary phase. [d] Addition of MgSO₄. [e] Reaction was performed with 2 mol % of catalyst. [f] Without any catalyst. Tf = trifluoromethanesulfonyl.

tinued to explore the generation of *o*-QMs with the 1,3-dioxole-substituted hydroxybenzyl alcohols **1k** and **1l**, which also gave good results. We have also evaluated different R² substitution at either *ortho* or *para* positions (**1m–p**) and all substrates furnished the corresponding products with good yields and good enantiomeric excesses. The absolute configuration of the products has been determined by X-ray single-crystal structure analysis of product **3a**.^[19] Furthermore, 5,5-dimethyl-1,3-cyclohexanedione (**2b**) has also been applied in this newly developed organocatalytic procedure and the desired product **3q** was obtained with 72 % yield and 86 % *ee* (Scheme 2). Noteworthy is that the cycloadduct **3q** is very similar to the structural motif found in important biologically



Scheme 2. Brønsted acid catalyzed asymmetric synthesis of important structural motifs with anticancer activity. M.S. = molecular sieves.

Table 2: Substrate scope of Brønsted acid catalyzed enantioselective addition/cyclization reaction.



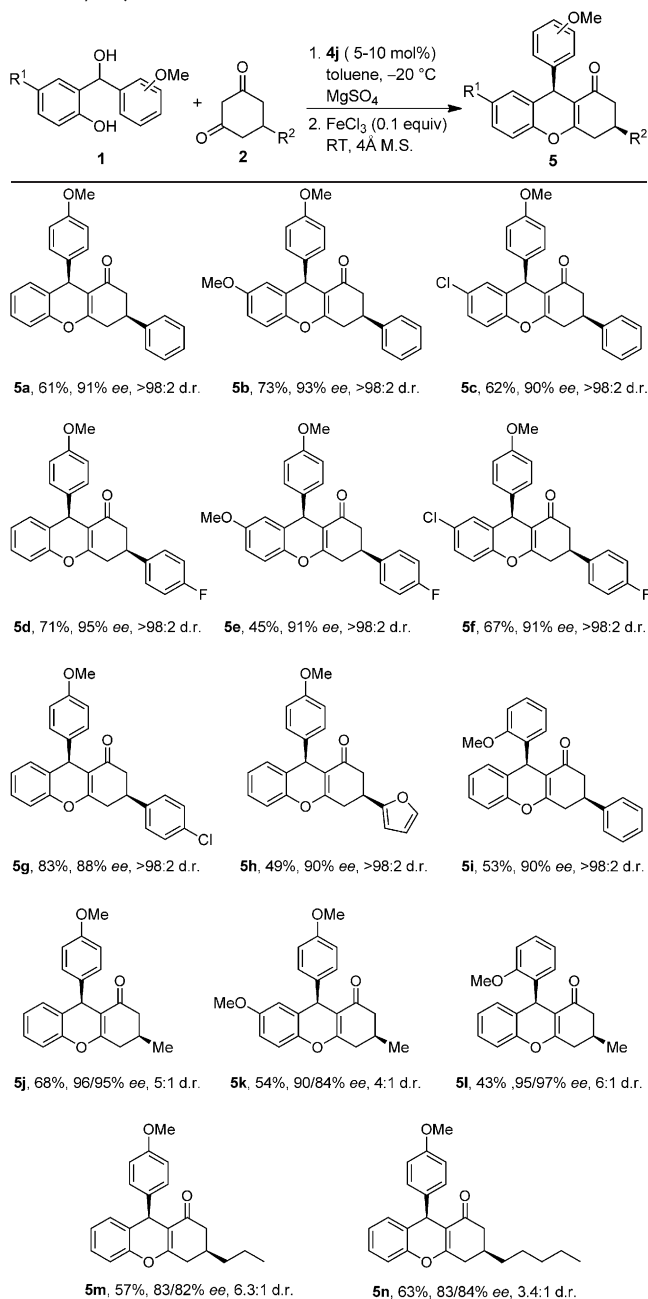
[a] Reactions were performed with the alcohol **1**, cyclohexane-1,3-dione **2a** (3 equiv), and 5 mol % **4h**. The solution was stirred at -10°C for 8 h, and then at RT until cyclization was complete.

active molecules with antiproliferative activity for human cancer.^[20]

After evaluating a wide array of *o*-QMs with 1,3-diketone nucleophiles (**2a,b**) which afforded the cycloadducts **3a–q** bearing a single stereocenter (Table 2 and Scheme 2), we considered the possibility of developing a protocol for the generation of products with a set of two stereocenters by using *meso*-5-monosubstituted-1,2-cyclohexanediones in the reaction. If this proposal was realized under Brønsted acid catalysis, valuable tetrahydro-1*H*-xanthen-1-one derivatives bearing stereocenters at the 3- and 9-positions would be obtained.

After optimizing the reaction conditions, this new desymmetrization strategy was tested for its generality. Essentially, high diastereomeric ratios and enantiomeric excesses for the desired cycloadducts bearing aromatic and heteroaromatic substituents, as well as aliphatic functional groups at the 9-position were obtained (Table 3). Firstly, *p*-methoxy-substituted hydroxybenzyl alcohols with different substituents (R¹) were used and the adducts **5a–c** were isolated as a single

Table 3: Substrate scope of Brønsted acid catalyzed enantioselective addition/desymmetrization reaction.

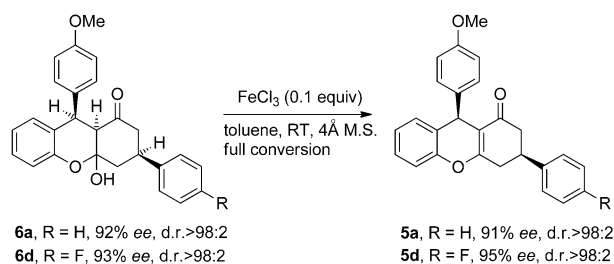


[a] Reactions were performed with the alcohol **1**, cyclohexane-1,3-dione **2**, and 5–10 mol % **4j**. The solution was stirred at -20°C until completion. The excess 1,3-dione nucleophile was removed and FeCl₃ (0.1 equiv), 4 Å M.S. and toluene were added and the solution was stirred at RT until completion.

diastereomer in good yields (61–73 %) and with excellent enantioselectivities (90–93 % *ee*). We then focused on employing different 5-aryl-substituted 1,3-cyclohexanedione nucleophiles in the reaction with various *o*-QMs and the corresponding adducts **5d–h** were obtained as single diastereomers in moderate to high yields (45–83 %) and excellent enantioselectivities (88–95 % *ee*).

We also prepared the *o*-methoxy-substituted hydroxybenzyl alcohol and the appropriate product **5i** was obtained as single diastereomer in 53 % yield and 90 % *ee*. Aliphatic groups in the 5-position of the 1,3-dione were also tolerated in this new desymmetrization protocol. Particularly noteworthy is the excellent enantioselectivity observed in the case of small methyl substituent on the dione nucleophile with different *o*-QMs substrates (**5j–l**; 90–96 % *ee*). 1,3-Diones with longer aliphatic carbon chains reacted efficiently and afforded the corresponding products **5m** and **5n** with slightly diminished diastereo- and enantioselectivities.

As the reaction is believed to follow an asymmetric Brønsted acid catalyzed 1,4-addition/cyclization pathway we tried to isolate the hemiacetal intermediate. Indeed, we were able to isolate and identify the proposed intermediates **6a** and **6d**. Subsequent subjection to FeCl₃ catalysis afforded the tetrahydroxanthene products **5a** and **5d** in full conversion and with retention of configuration (Scheme 3). The configuration at the 9-position in the products **5** has been assigned in analogy to the products **3**. The configuration at the 3-position has been assigned according to NOE experiments, which showed a *cis* relationship for the protons in the 3- and 9-positions.^[19]



Scheme 3. Dehydration of the intermediates **6a** and **6d**.

A possible transition-state model to explain the absolute configuration of the tetrahydroxanthene products through multiple hydrogen-bond interactions between the chiral catalyst and substrate is proposed (Figure 2). This arrangement provides a rigid environment for the asymmetric reaction to occur. The triisopropyl phenyl groups at the 3,3'-positions of the catalyst block the backside attack of the nucleophile, thus affording the *R*-configured stereocenter in the Michael addition. The high diastereoselectivity can be rationalized by coordination and attack of the substituted 1,3-diketone from the less hindered face, thus affording the thermodynamically more favored single diastereomer after dehydration.

In summary, we have developed a new highly enantioselective synthesis of 9-substituted tetrahydroxanthenes by means of asymmetric Brønsted acid catalysis.^[21] A chiral

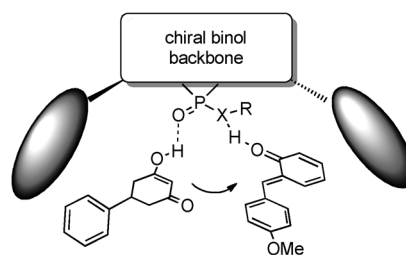


Figure 2. Plausible transition states for the chiral Brønsted acid catalyzed reaction.

binol-based *N*-triflylphosphoramidate was found to promote the in situ generation of *o*-QMs and their subsequent asymmetric reaction with 1,3-cyclohexanedione to deliver the desired products with excellent enantioselectivities. In addition, a highly enantio- and diastereoselective Brønsted acid catalyzed desymmetrization of 5-monosubstituted-1,3-dicarbonyl substrates with *o*-QMs has been developed. A broad range of valuable tetrahydroxanthenes with two embedded distant stereocenters were synthesized according to this newly developed method. Notably, a chiral binol phosphoric acid catalyst proved to participate extensively in this catalytic cycle, through generation of *o*-QMs, activation of 1,3-dicarbonyl compounds, control of Michael addition, and desymmetrization of *meso* 1,3-dicarbonyl compound. Given the value of the products and the wide applicability of *o*-QMs in organic synthesis, further investigation regarding the detailed mechanism and utilization of this organocatalytic procedure in the preparation of natural products and bioactive compounds^[22] is underway.

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