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Asymmetric Catalysis

Catalytic Asymmetric Addition of Meldrum's Acid, Malononitrile and 1,3-Dicarbonyls to *ortho*-Quinone Methides Generated In Situ Under Basic Conditions

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Abstract: A new approach to the utilization of highly reactive and unstable *ortho*-quinone methides (*o*-QMs) in catalytic asymmetric settings is presented. The enantioselective reactions are catalysed by bifunctional organocatalysts, and the *o*-QM intermediates are formed in situ from 2-sulfonylalkyl phenols through base-promoted elimination of sulfinic acid. The use of mild Brønsted basic conditions for transiently generating *o*-QMs in catalytic asymmetric processes is unprecedented, and allows engaging productively in the reactions nucleophiles such as Meldrum's acid, malononitrile and 1,3-dicarbonyls. The catalytic transformations give new and general entries to 3,4-dihydrocoumarins, 4*H*-chromenes and xanthenones. These frameworks are recurring structures in natural product and medicinal chemistry, as testified by the formal syntheses of (*R*)-tolterodine and (*S*)-4-methoxydalbergione from the catalytic adducts.

The high energy gain due to aromatization in reactions of quinone methides[1] (2- and 4-alkenyl cyclohexadienones, *o*- and *p*-QMs) with 2π systems generally define these unstable species as "highly reactive", or even as "ephemeral" and "elusive", synthetic intermediates.[2] Although their relevance in biological processes is undisputable,[1] *o*-QMs have been termed as a "synthetic enigma".[2a] In fact, reports describing the utilization of QMs in catalytic asymmetric settings[3] have been scarce until very recently, highlighting the challenge of taming their high reactivity/instability. Significant breakthroughs have exploited the possibility of stabilizing the electron-poor triene core of QMs by electron-donating substituents, up to a point that isolation is possible. Accordingly, *o*- and *p*-QMs multisubstituted with electron-donating groups have been treated with nucleophiles under the action of different catalysts.[4]

However, to overcome the inherent limitation in scope of using stabilized substrates, conditions compatible with both formation of a reactive QM and a catalytic asymmetric reaction, have to be devised.[5] This challenging task has been recently met by exploiting different strategies for the transient generation of an *o*-QM intermediate. Available examples involve palladium catalysed oxidative additions to *ortho*-hydroxy styrenes,[6,7] desilylation–halide elimination of *O*-silyl 2-haloalkyl phenols[8] and pyrones,[9] alcohol elimination of 2-alkoxyalkyl phenols,[10] and dehydration of the corresponding benzylic alcohols.[11] The latter approach, wherein chiral Brønsted acid catalysts promote both dehydration and addition to the thus formed *o*-QM, has proven to be particularly flexible, and has been very recently applied to electron-rich aromatics,[12] enamides,[13] and 1,3-dicarbonyl compounds (mostly diketones)[14] as nucleophilic reaction partners.

Herein, we report a new approach to the utilization of *o*-QMs in asymmetric catalysis, by demonstrating that enantioselective additions of 1,3-dicarbonyls promoted by Cinchona-derived organocatalysts **3**[15] can be combined with the in situ generation of sensitive *o*-QM from 2-(arylsulfonyl)alkyl phenols[16] **1**–**2** (Scheme 1). While high variability in *o*-QM structure is provided by their in situ production, the unprecedented exploitation of Brønsted basic conditions for both *o*-QM formation by sulfinic acid elimination and ensuing enantioselective reaction gives the present approach a scope fully complementary to other methodologies. Not only the previously reported[14] 1,3-diketones and 3-ketoesters, but also Meldrum's acid and malononitrile can be productively engaged in the asymmetric transformation. Cyclizations at the phenolic oxygen follow the nucleophilic additions, affording 3,4-dihydrocoumarins **4** and 4*H*-chromenes **5** and **6**. These structures are privileged scaffolds in medicinal and natural product chemistry (vide infra).[17]

At the outset of this work, on the basis of our experience[18] and related literature data on the in situ generation of imines and alkylidenendolenines by sulfinic acid elimination,[19] we explored combinations of bifunctional organic catalysts, inorganic bases, and various common active methylene compounds in the reaction with the 5-methoxysalicylaldehyde derived sulfone **1a**. In line with previous tactics,[10] we focused on this sulfone **1a** for our initial studies reasoning that its methoxy group would favour formation of the *o*-QM intermediate, and stabi-

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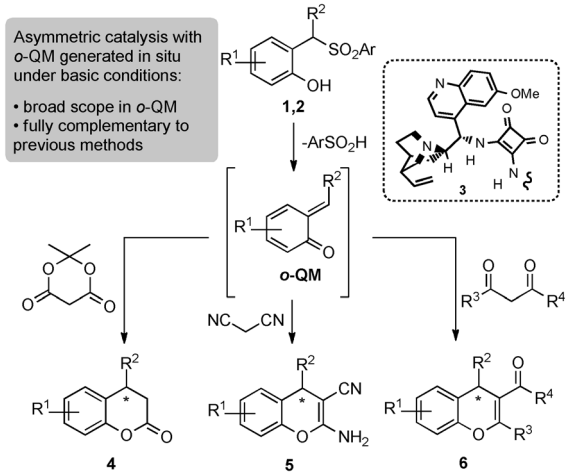
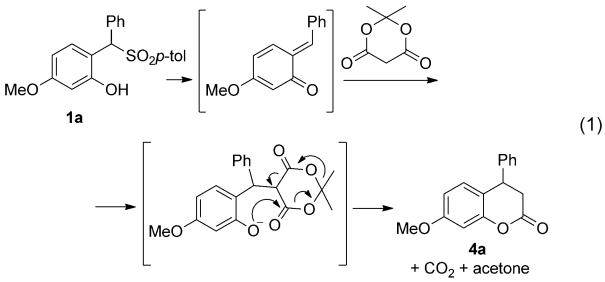


Scheme 1. Catalytic asymmetric additions of 1,3-dicarbonyl compounds to *o*-QMs generated in situ by sulfinic acid elimination.

lize it.[1d] After considerable experimentation, encouraging reactivity was observed with Meldrum's acid, which furnished the 3,4-dihydrocoumarin **4a**, resulting from cyclization and ensuing decarboxylation of the intermediate adduct [Eq. (1)].[20]

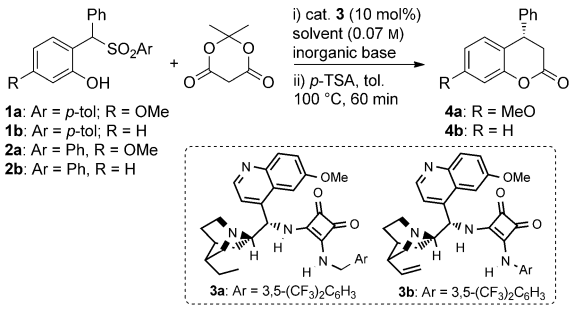
A short screening of different catalysts pointed to 9-amino(9-deoxy)*epi* dihydroquinine squaramide[21] catalyst **3a** as a promising structure, delivering the hit result reported in Table 1 (entry 1). The crude mixtures were always treated with *p*-TSA, to ensure lactonization to **4a** of the corresponding open chain carboxylic acid, sometimes observed in small amounts in the crude. The importance of the inorganic base was demonstrated by the results shown in entries 1–4. While lower enantioselectivities with bases stronger than bicarbonate could be attributed to a background racemic reaction, the lower conversions observed with nonaqueous bases were ascribed to their poor efficiency in catalyst regeneration.[22] Using aqueous $NaHCO_3$, an increase in conversion and enantioselectivity was observed by heating the reaction to 40 °C, and switching to the aniline-derived catalyst **3b** (entry 5), which performed best amongst a series of related structures (see the Supporting Information). Even though better results could be obtained using DCE as solvent (entry 6), we were faced with great disappointment when we purified product **4a** to determine the yield of the reaction, which was unacceptably low. A large number of experiments directed



(1)

at its improvement through changing the various reaction parameters (solvent, catalyst loading and type, temperature, concentration, reaction time, type and amount of inorganic base, order and rate of the additions, excess of Meldrum's acid), proved to be unfruitful. Furthermore, the reaction with the unsubstituted sulfone **1b**, lacking the stabilizing methoxy group, proved to be sluggish, with only 61% conversion reached after prolonged reaction time, even when using 5 equiv of Meldrum's acid (entry 7). The unsatisfactory results obtained with these two sulfones **1** were ascribed to two opposite reasons,[1d] which we thought give enough merit to the definition of *o*-QMs as a "synthetic enigma".[2a] In the case of the methoxy derivative **1a**, the rapid formation of the *o*-QM intermediate, accompanied by its plausibly poor reactivity, caused its accumulation in the reaction medium. Thus, degradation competed with the desired enantioselective addition, resulting in low yield. In the case of the unsubstituted derivative **1b**, decomposition was not an issue, since the highly reactive *o*-QM formed only in small amounts. However, its formation was so disfav-

Table 1. Selected optimization results in the reaction with Meldrum's acid.[a]



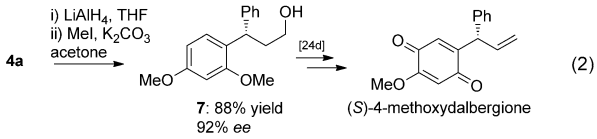
Entry	1, 2	Solv.	Base [equiv]	3	*T* [°C]	*t* [h]	Conv.[b] [%]	*ee*[c] [%]
1	**1a**	tol.	$NaHCO_3$ aq. 10% [10]	**3a**	RT	24	**4a**, 41	72
2	**1a**	tol.	K_2CO_3 aq. 5% [3]	**3a**	RT	24	**4a**, 44	48
3	**1a**	tol.	Na_2CO_3 [5]	**3a**	RT	24	**4a**, 30	69
4	**1a**	tol.	K_2CO_3 [5]	**3a**	RT	24	**4a**, 29	80
5	**1a**	tol.	$NaHCO_3$ aq. 10% [10]	**3b**	40	22	**4a**, >95	92
6	**1a**	DCE	$NaHCO_3$ aq. 10% [10]	**3b**	40	18	**4a**, >95 (47)[d]	93
7[e]	**1b**	DCE	$NaHCO_3$ aq. 10% [10]	**3b**	40	96	**4b**, 61	92
8[e]	**2b**	DCM	$NaHCO_3$ aq. 10% [10]	**3b**	RT	70	**4b**, >95	93
9[e]	**2a**	DCM	$NaHCO_3$ aq. 5% [10]	**3b**	RT	20	**4a**, >95 (76)[d]	94

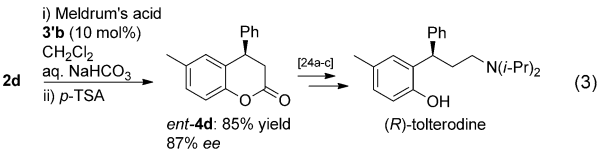
[a] Conditions: i) sulfone **1**, **2** (0.05 mmol), Meldrum's acid (0.10 mmol), cat. **3** (0.005 mmol, 10 mol%), solvent (0.75 mL), inorganic base, then HCl aq. 0.1 M, filtration of the organic phase on Celite®, evaporation; ii) toluene, cat. *p*-TSA, 100 °C, 60 min. [b] Determined by ^{1}H NMR spectroscopy after the first step (considering **4** + carboxylic acid). [c] Determined by chiral stationary phase HPLC. [d] Yield of product **4** purified by chromatography on silica gel. Reactions performed on 0.10 scale. [e] 5 equiv of Meldrum's acid were used.

oured that conditions compatible with the sensitive catalytic asymmetric step could not be devised. Pleasingly and unexpectedly, we discovered a solution applicable to both cases, observing that a very subtle change at the aryl group of the sulfone, swapping the *p*-tolyl for a phenyl, gave a surprisingly dramatic improvement over its leaving group ability.[23] Thus, the unsubstituted phenylsulfone **2b** fully converted even at RT, affording the product **4b** in good yield and improved enantioselectivity (entry 8). On the other hand, the opportunity of producing the sensitive methoxy substituted *o*-QM intermediate from sulfone **2a** at RT, instead of 40 °C, was sufficient to avoid most of the degradation pathway, resulting in improved yield of the corresponding product **4a** (entry 9).

We then explored the applicability of these conditions to other *o*-QMs, by studying the reaction of Meldrum's acid with various sulfones **2a**–**k**. As shown in Table 2, adducts **4a**–**f** bearing substituents with different electronic properties at the phenolic ring were obtained with good results, in terms of both yields and enantioselectivities (Table 2, entries 1–6). Thus, the non-obvious tolerance of the reaction to various degrees of *o*-QM stability/reactivity was demonstrated. Variations at the benzylic substituent, which also can influence to some extent the characteristics of the *o*-QM, were then briefly investigated. As shown in entries 7–11, both electron-donating and -withdrawing groups at this aromatic substituent were well tolerated, as the corresponding 3,4-dihydrocoumarins **4g**–**k** were obtained with good results.

4-Aryl-3,4-dihydrocoumarins **4** are highly valuable synthetic intermediates.[24] For example, reduction of the lactone in adduct **4a** followed by methylation gave the alcohol **7** [Eq. (2)], convertible in two steps into (*S*)-4-methoxydalbergione,[10,24d] a natural quinone product isolated from *Dalbergia* tropical plants. Conversely, compound *ent*-**4d**, obtainable using catalyst **3′b** derived from quinidine, quasi-enantiomeric to **3b** [Eq. (3)], is the key intermediate in several asymmetric syntheses of (*R*)-tolterodine,[24a–c] the active ingredient of the commercial antimuscarinic drug Detrol®, and **4j** is the precursor of the potent endothelin antagonists SB-209670 and SB-217242 [Eq. (4)].[24e,f]





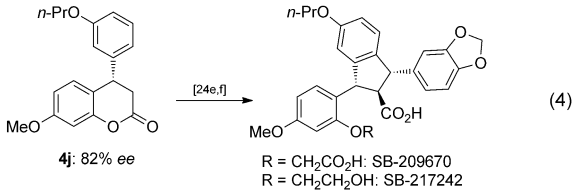
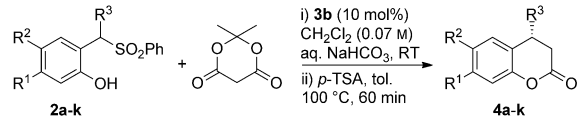


Table 2. Variation in the *o*-QM precursor **2** in the reaction with Meldrum's acid.[a]

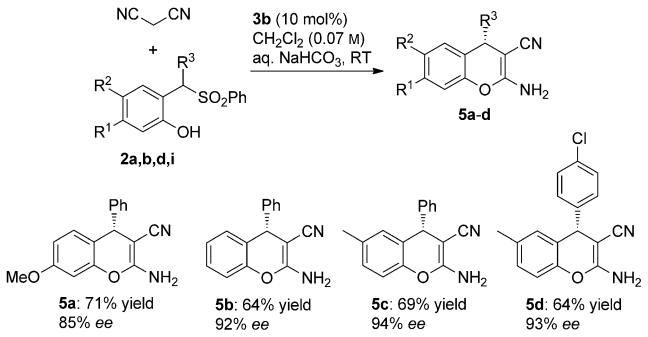


Entry	2	R^1	R^2	R^3	4, Yield[b] [%]	*ee*[c] [%]
1	**2a**	OMe	H	Ph	**4a**, 76	94
2	**2b**	H	H	Ph	**4b**, 83	93
3	**2c**	Me	H	Ph	**4c**, 77	95
4	**2d**	H	Me	Ph	**4d**, 82	96
5	**2e**	H	Br	Ph	**4e**, 76	93
6[d]	**2f**	$O(CH_2)O$		Ph	**4f**, 75	88
7	**2g**	H	H	4-$(MeO)C_6H_4$	**4g**, 79	88
8	**2h**	H	H	4-ClC_6H_4	**4h**, 82	95
9	**2i**	H	Me	4-ClC_6H_4	**4i**, 81	95
10	**2j**	OMe	H	3-(*n*-PrO)C_6H_4	**4j**, 74	82
11	**2k**	H	Me	2-$(MeO)C_6H_4$	**4k**, 70	92

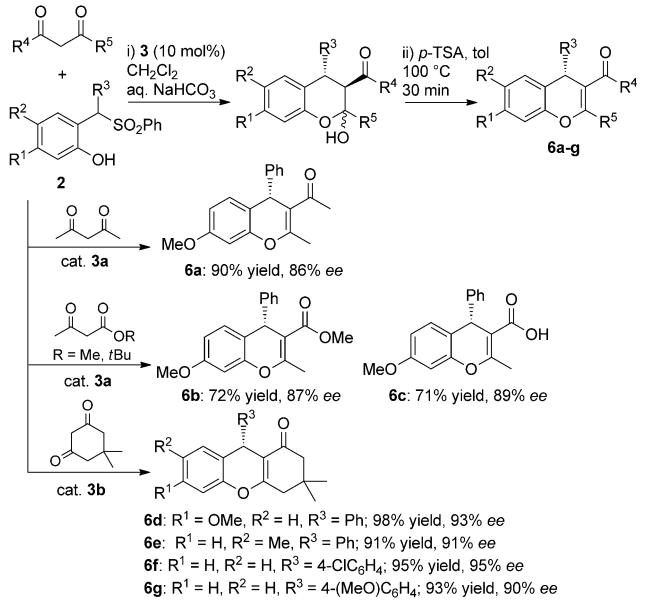
[a] Conditions: i) sulfone **2** (0.10 mmol), Meldrum's acid (0.50 mmol), cat. **3b** (0.010 mmol, 10 mol%), CH_2Cl_2 (1.42 mL), aq. $NaHCO_3$ (5 or 10%, 5.0 mmol), RT, 18–72 h then HCl aq. 0.1 M, filtration of the organic phase on Celite®, evaporation; ii) toluene, cat. *p*-TSA, 100 °C, 60 min. [b] Yield of product **4** purified by chromatography on silica gel. [c] Determined by chiral stationary phase HPLC. [d] 20 mol% of **3b** were used.

Then, we studied the reaction with other nucleophiles amenable to activation by catalysts **3**. Performing the reaction under the same conditions used for Meldrum's acid, we were pleased to discover that malononitrile reacted well with various *o*-QM precursors **2** (Scheme 2). The initial adducts cyclized spontaneously, without requiring any additional treatment, furnishing cleanly the corresponding 4*H*-chromenes **5a**–**d**. Also in this case, the reaction proved to be tolerant to various substituents at the aromatic rings. Interestingly, the products **5** feature a specific 2-amino-4*H*-4-arylchromene-3-carbonitrile framework, which has been found to possess some promising apoptosis-inducing activity.[25] To our knowledge, the present method represents the first general catalytic enantioselective approach to this class of 4*H*-chromenes.

We have also explored the reaction with 1,3-diketones and 1,3-ketoesters (Scheme 3). In these reactions, an equilibrating diastereomeric mixture of hemiacetal adducts was obtained in the crudes, which could be dehydrated to 4*H*-chromenes and xanthenones **6** by treatment with *p*-TSA. These acidic conditions caused ester cleavage in the case of product **6c** derived from *tert*-butyl acetoacetate. The reactions with acetylacetone and 3-ketoesters proved to be somewhat less robust compared to the previous nucleophiles explored, with good results being obtained only with the methoxy substituted sulfone **2a**. Furthermore, better enantioselectivities were obtained by using the benzylamine substituted catalyst **3a** (Table 1). In contrast, excellent reactivity and tolerance to various substitution



Scheme 2. Catalytic enantioselective additions of malononitrile to *o*-QM generated in situ from sulfones **2**.



Scheme 3. Catalytic enantioselective additions of 1,3-diketones and 3-ketoesters to *o*-QM generated in situ from sulfones **2**.

patterns was regained in the reactions with dimedone, which afforded the corresponding xanthenones **6d–g** with very good results.

The specific rotations of **4d**, **4j**, **6g** and **7** are in agreement with reported literature data for the *S* enantiomeric products. Additionally, the same *S* absolute configuration was inferred on compounds **5** by comparison of calculated (TD-DFT) with experimental ECD spectra (see the Supporting Information).[26]

In conclusion, we have developed the first example of a catalytic asymmetric reaction with *o*-QMs which exploits basic conditions for the in situ generation of these challenging intermediates.[27] This approach gives full complementarity to previous methodologies,[6–14] and allows to perform the enantioselective additions of different nucleophiles with good results and broad substrate scope, giving a new and general access to valuable 3,4-dihydrocoumarin and 4*H*-chromene scaffolds.

Acknowledgements

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Keywords: asymmetric catalysis · enantioselectivity · organocatalysis · quinone methides · sulfones

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Asymmetric Catalysis

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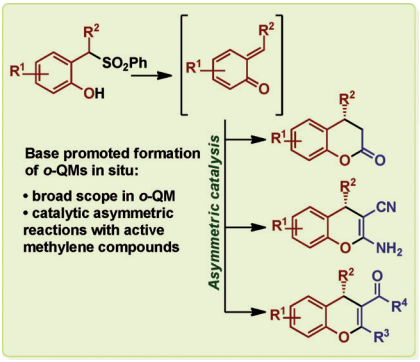
Catalytic Asymmetric Addition of Meldrum's Acid, Malononitrile and 1,3-Dicarbonyls to *ortho*-Quinone Methides Generated In Situ Under Basic Conditions



Challenging substrates: The generation in situ of *ortho*-quinone methides (*o*-QMs) through sulfinic acid elimination was combined for the first time with an organocatalytic process (see scheme). This combination allowed the engagement of sensitive and unstable *o*-QMs in asymmetric reactions with active methylene compounds, under the promotion of bifunctional catalysts, giving access to 2,3-dihydrocoumarins, 4*H*-chromenes and xanthen-1-ones.