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Asymmetric Phosphine-Catalyzed [4 + 1] Annulations of *o*-Quinone Methides with MBH Carbonates

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Abstract. Chiral dihydrobenzofuran units are frequently present in molecules with significant biological and pharmaceutical activities. Herein, we present the first enantioselective formal [4 + 1] annulation of Morita−Baylis−Hillman carbonates with *o*-quinone methides (*o*-QMs) catalyzed by a newly designed chiral phosphine catalyst. Under the mild and eco-friendly conditions, a wide range of polysubstituted dihydrobenzofurans were obtained in good yields with excellent enantioselectivities.

Keywords:[4+1] Annulation; chiral phosphines; asymmetric catalysis; MBH carbonates; *ortho*-quinone methides

Chiral dihydrobenzofuran scaffolds, which represent one class of the most important heterocycle, are important building blocks in organic synthesis and widely exist in natural products and bioactive molecules, i.e. anti-inflammatory, CB2 receptor agonist, oral antioxidant (Figure 1).[1] Thus, the development of new methods, especially asymmetric ones, for the construction of these important target motifs has recently attracted considerable interest.

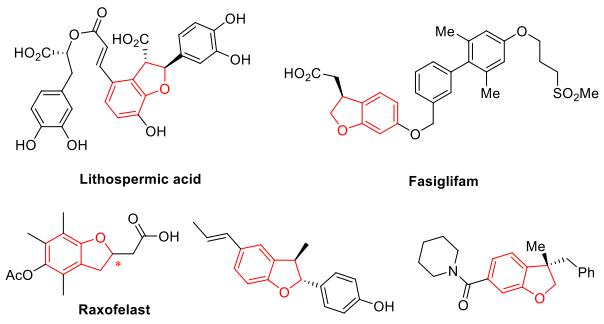
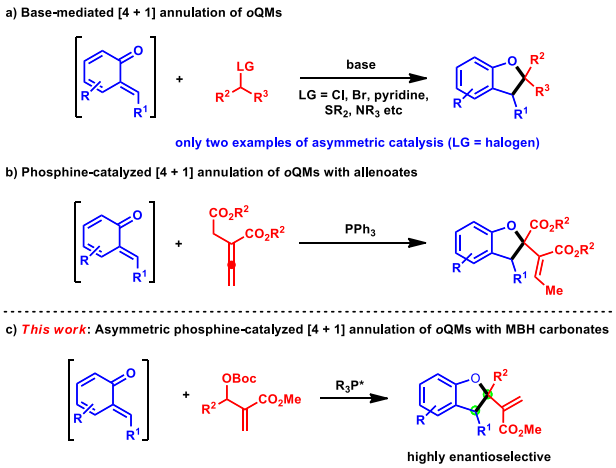


Figure 1. Dihydrobenzofuran motif in natural products and bioactive molecules.



Scheme 1. Dihydrobenzofuran synthesis via [4 + 1] cyclizations of *o*-QMs

Recently, quinone methides (QMs)[2] have emerged as common-used building blocks or versatile intermediates in organic synthesis. *p*-Quinone methides (*p*-QMs) have been normally used as the acceptor for 1,6-addition or 1,8-addition reactions,[3] and *o*-quinone methides (*o*-QMs)[4,5] were very successfully employed for various [4 + n] cyclizations.[6-9] However, most of the annulations of *o*-QMs were [4 + 2] with electron-rich alkenes, delivering the chroman skeletons.[6] The [4 + 1] annulation of *o*-QMs with C1 synthons is the straightforward approach to construct dihydrobenzofuran scaffolds, however, only a few examples of [4 + 1] cyclizations are reported.[9] For example, the carbon nucleophile with leaving group, e.g. sulfur ylides,[9a-d] pyridinium methylides,[9e] ammonium ylides,[9f] *α*-halogen carbonyl compounds,[9h-i] were successfully utilized as C1 synthons to perform [4 + 1] annulations with *o*-QMs (Scheme 1a). Very recently, the formal [4 + 1] reaction of *o*-QMs and *α*-branched allenoates as C1 synthons has been developed (Scheme 1b).[9g] In spite of these elegant achievements, the asymmetric

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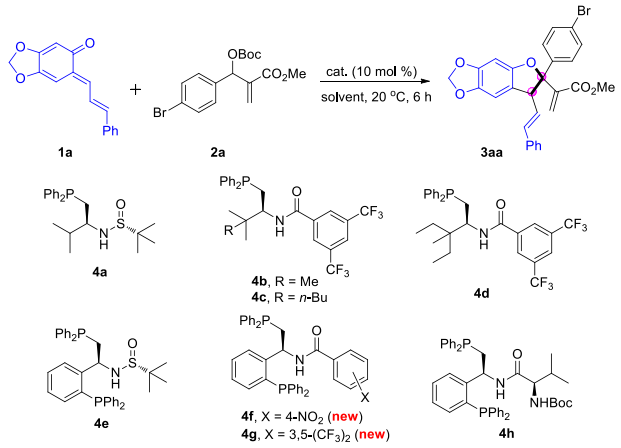
catalytic version of [4+1] cyclizations of *o*-QMs with C1 synthons are still rare and the leaving groups are limited to halogen.[9h-i]

Table 1. Optimization of Reaction Conditions[a].



entry	cat	solvent	yield (%)[b]	dr (%)[c]	ee (%)[d]
1	**4a**	toluene	NR	-	-
2	**4b**	toluene	56	1:1.4	99/29
3	**4c**	toluene	52	1:1.4	89/60
4	**4d**	toluene	56	1:1	60/39
5	**4e**	toluene	trace	-	-
6	**4f**	toluene	72	1.3:1	94/62
7	**4g**	toluene	83	1:1.5	99/68
8	**4h**	toluene	72	1:2.3	90/68
9	**4g**	THF	56	1:2.5	92/89
10	**4g**	DCM	23	1:3	98/90
11	**4g**	DCE	88 (85)	1:2.1	99/90
12	**4g**	Et_2O	43	1:1.2	90/79
13	**4g**	1,4-dioxane	trace	-	-
14	**4g**	$CHCl_3$	80	1:1	98/82

[a] Unless otherwise stated, all reactions were carried out using **1a** (0.2 mmol), **2a** (0.24 mmol), **4** (10 mol%) in solvent (2 mL) at 20 °C for 6 hours. [b] Yields were determined by ^{1}H-NMR, using CH_2Br_2 as internal standard. Numbers given in parathesis are isolated yield. [c] Determined by crude ^{1}H-NMR. [d] Determined by HPLC.

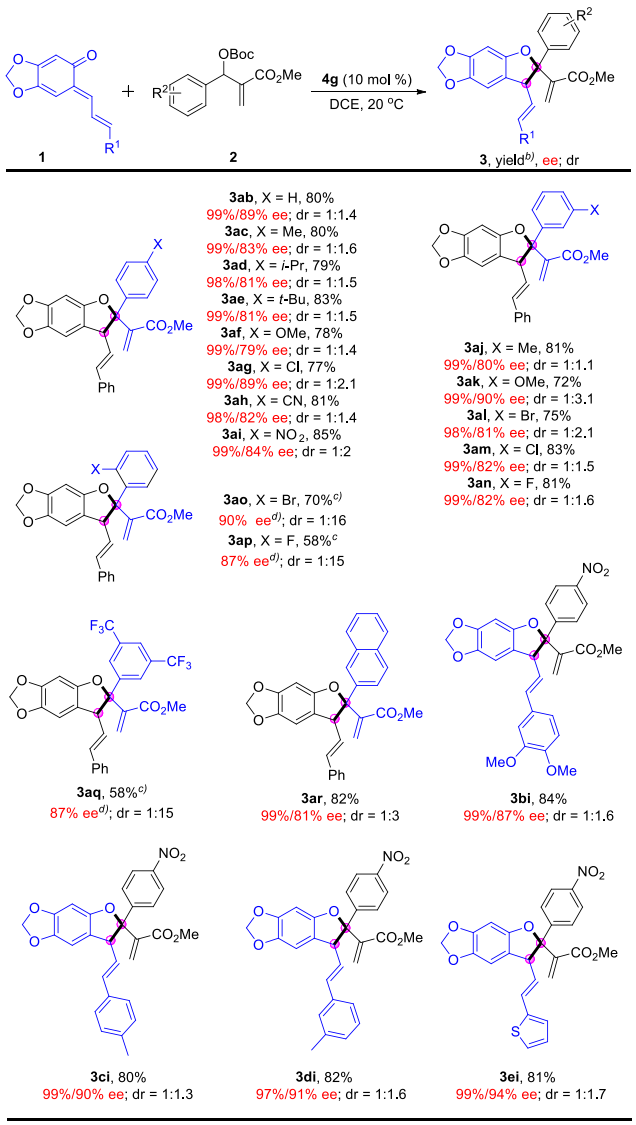
Meanwhile, asymmetric phosphine-catalyzed annulation reaction provides a highly powerful and efficient approach for the construction of highly functionalized carbocyclic or heterocyclic compounds.[10,11] In this context, Morita−Baylis−Hillman (MBH) carbonates[12,13] are readily available and versatile reactants, which can act as C1 synthons in annulations promoted by phosphine catalysts. In 2010, we developed the first phosphine-catalyzed [4 + 1] annulation of *α,β*-unsaturated ketones (enones) with MBH carbonates, leading to the constuction of 2,3-dihydrofurans in racemic manner.[14] As part of our ongoing interest in the development of novel chiral phosphine catalysts and the new reactions catalyzed by phosphine,[15] we wondered whether the reaction of *o*-QMs with MBH carbonates could undergo the similar pathway with acyclic enones. If so, the asymmetric phosphine-catalyzed [4 + 1] annulation of *o*-QMs with MBH carbonates may be realized to afford optically active dihydrobenzofuran scaffolds.

With this hypothesis in mind, *o*-QMs **1a** and MBH carbonate **2a** were chosen as model substrates for this [4 + 1] annulation reaction. Various chiral bifunctional phosphine catalysts **4a-4h**, which are easily prepared from chiral sulfonamide in a few steps, were tested (Table 1). The Xiao-Phos **4a** with a chiral sulfonamide as the H-bonding donor could not catalyze this reaction (Table 1, entry 1). To our delight, when the catalyst **4b** with 3,5-bistrifluoromethyl benzoyl amide instead of sulfonamide was used, the reaction proceeds smoothly to afford the desired [4 + 1] product **3aa** in moderate yield with 1:1.4 dr and 99%/29% ee (Table 1, entry 2). This result indicates that the catalyst with stronger H-bonding was beneficial to the yield and stereoselectivity. We then turned to examine the effect of alkyl substituents on *α*–position of nitrogen (**4c**−**4d**), but the yield and stereoselectivity cannot be improved (Table 1, entries 3-4). Another phosphine catalyst developed by us Wei-Phos **4e** was also tested, which gave only trace amount of product (Table 1, entry 5). Gratifyingly, 83% yield with 99%/68% ee and 1:1.5 dr could be obtained when the modified Wei-Phos **4g** using 3,5-bis(trifluoromethyl) benzoyl amide instead of sulfonamide was used (Table 1, entry 7). Other H-bonding donors cannot improve the results.[16] After solvent screening (Table 1, entries 9 14), the best result was obtained when the reaction was carried out in DCE (Table 1, entry 11). The absolute configuration of the minor isomer of **3aa** was determined by single-crystal X-ray diffraction analysis.[17]

With the optimal conditions in hand, we next examined the MBH carbonate scope of this asymmetric [4 + 1] annulation reaction. As shown in Table 2, *o*-QMs **1a** reacted with a variety of MBH carbonates **2** with electron-donating groups and electron-withdrawing groups (R^2), including alkyl, alkoxyl, halogen and cyano etc., on the *para*-position of phenyl ring, leading to the corresponding dihydrobenzofuran **3ab-3ai** in good yields with good enantioselectivities (Table 2). The substituents on the *meta*-position of phenyl ring had no effect on the reactivity and enantioselectivity, either (Table 2, **3aj-3an**). It was noteworthy that the reaction of MBH carbonates **2o-2p** with the substituents on the *ortho*-position of phenyl ring showed a slightly lower yields and enantioselectivity but much higher diastereoselectivities (up to 1:16) than that of **2a** (Table 2, **3ao-3ap**). The steric hindrance effects of *ortho*-substituents might account for this result. The 3,5-bis(trifluoromethyl) group exhibited the similar effect with *ortho*-substituents on this transformation (Table 2, **3aq**). 2-Naphthyl was also compatible with this [4 + 1] cyclization (Table 2, **3ar**). Furthermore, we turned to examine the scope of *o*-QMs for this transformation. Gratifyingly, the reaction of MBH

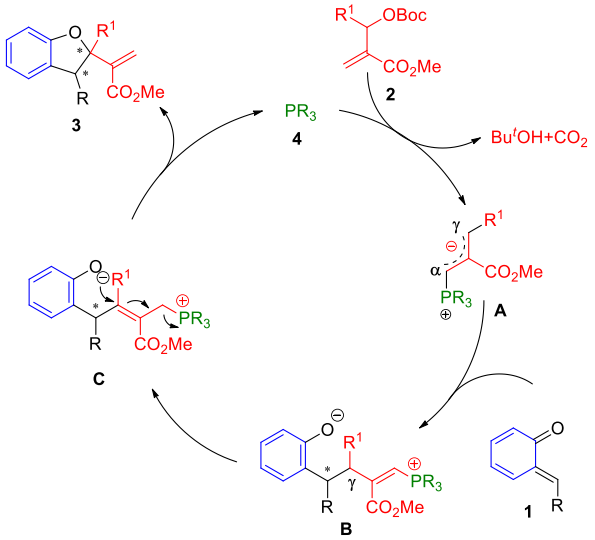
carbonates **2i** with various *o*-QMs **1b-1e**, including substituted phenyl ring and heterocycle, worked well, furnishing the desired dihydrobenzofurans **3bi-3ei** in good yields with good enantioselectivities (Table 2).

Table 2. Phosphine-Catalyzed Asymmetric [4+1] Annulation of *o*-QMs with MBH Carbonates [a].



[a] Unless noted, all reactions were carried out using **1** (0.2 mmol), **2** (0.24 mmol), **4g** (10 mol %) in DCE (2 mL) at 20 °C. [b] Total yields of two isolated isomers. [c] Yield of isolated single isomer. [d] ee of the major isomer.

On the basis of the above results and previous relevant studies, a plausible catalytic cycle for this phosphine-catalyzed [4 + 1] cyclization is outlined in Scheme 2. Initially, chiral phosphine catalyst **4** acted as an organocatalyst to activate MBH carbonates **2**, affording an allylic phosphorus ylide **A**. Then, intermediate **A** would attack *o*-QMs **1** via Michael addition, in which step there are two possible reigoselectivities (*α*- or *γ*- selective). In this case, ylide **A** attacked *o*-QMs **1** with a γ-selectivity to form intermediate **B**, which could transform to intermediate **C** via direct or indirect 1,3-H shift. Finally, the intramolecular O anion attacked the double bond and eliminated the catalyst to obtain the target product and realize the catalytic cycle.



Scheme 2. Proposed catalytic cycle

In summary, we have developed the first asymmetric [4 + 1] annulation reaction of *o*-QMs and MBH carbonates catalyzed by a novel chiral phosphine catalyst. This method provides an efficient and concise strategy for the construction of chiral 2,3-dihydrobenzofuran derivatives. The salient features of this reaction include broad substrate scope, mild reaction conditions, high enantioselectivity and convenient operation. This reaction will not only enrich asymmetric cyclizations of *o*-QMs, but also broaden the utilization of MBH adducts. Furthermore, this reaction encourage us to develop novel phosphine catalysts based on chiral sulfonamide.

Experimental Section

A stirred solution of **1a** (50.5 mg, 0.2 mmol), **2a** (89.0 mg, 1.2 equiv) and **4g** (14.5 mg, 0.02 mmol) in DCE (2 mL) at 20 °C. The mixture was stirred at this temperature for 6 hours. After completion of the reaction, the reaction mixture was directly purified by silica gel chromatography using petroleum ether/EtOAc = 20/1 as the eluent to afford two isolated isomers of the desired products **3aa**.

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[17] CCDC 1850205 (minor isomer of **3aa**).

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