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Dearomative [4+2] Cycloaddition of Oxindole-Embedded *ortho*-Quinone Methides with 2,5-Dialkylfurans

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Abstract. 2,5-Dialkylfurans were facilely converted to pharmaceutically significant spiro[chroman-4,3'-oxindole] scaffolds *via* an organocatalytic dearomative [4+2] cycloaddition with oxindole-embedded *ortho*-quinone methides. This method featured mild reaction conditions, simple operation, good yields, and excellent diastereoselectivities.

Keywords: 2,5-dialkylfuran; spirooxindole; oxindole-embedded *o*-QMs; dearomatization; [4+2] cycloaddition

Spirooxindoles are privileged structural motifs in a wide range of natural products and pharmaceuticals with intriguing bioactivities (Figure 1).[1] Owing to their great significance, a large number of protocols have been developed to build up such scaffolds.[2] For instance, a quantity of methods dealt with the construction of spiro[chroman-3,3'-oxindole] frameworks *via* an *oxa*-Michael-Michael cyclization, in which oxindole components served as 2π synthons.[3] Nevertheless, there are only sporadic reports with regard to the assembly of spiro[chroman-4,3'-oxindole] scaffolds,[4] in spite of their significant

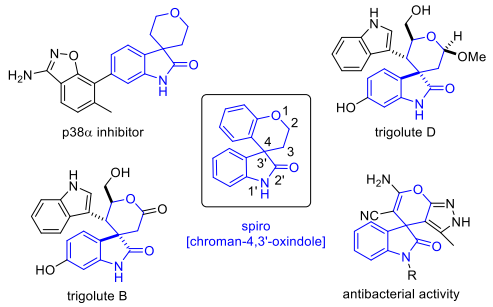
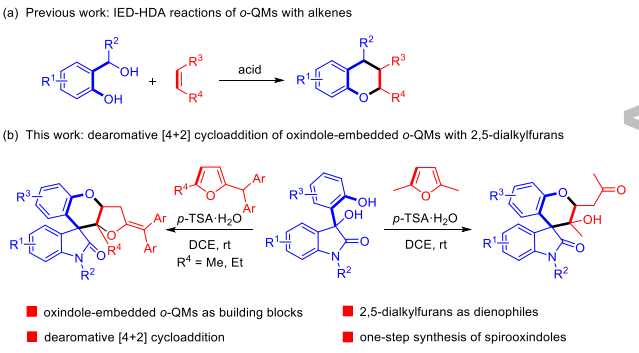


Figure 1. Representative bioactive molecules containing spirooxindoles.

contribution as core structures of numerous naturally occurring and medicinal molecules (Figure 1). Consequently, it is appealing to develop new synthons and cyclization strategies for one-step construction of spiro[chroman-4,3'-oxindole] scaffolds from readily available starting materials.

ortho-Quinone methides (*o*-QMs) are highly reactive intermediates for the synthesis of complex natural products and bioactive compounds.[5] With rearomatization as a driving force, *o*-QMs typically serve as electron-deficient dienes to participate in inverse-electron-demand hetero-Diels–Alder (IED–HDA) reactions (Scheme 1a).[6] However, the limited kinds of *o*-QMs and dienophiles restricted their applications in the assembly of molecular diversity and complexity, which posed a formidable challenge. To address this challenge, we rationally designed a new type of oxindole-embedded *o*-QMs and envisaged that a dearomative [4+2] cycloaddition of these *o*-QMs with 2,5-dialkylfurans would occur, thus providing a new synthetic option to spiro[chroman-4,3´-oxindole] scaffolds (Scheme 1b). In this strategy, 2,5-dialkylfurans would act as novel



Scheme 1. IED-HDA reaction of *o*-QMs and dearomative [4+2] cycloaddition of oxindole-embedded *o*-QMs with 2,5-dialkylfurans.

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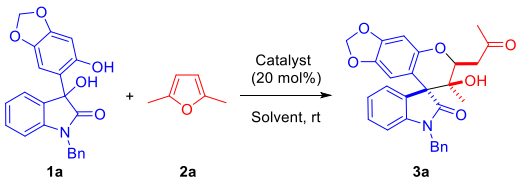
Table 1. Optimization of the reaction conditions[a]

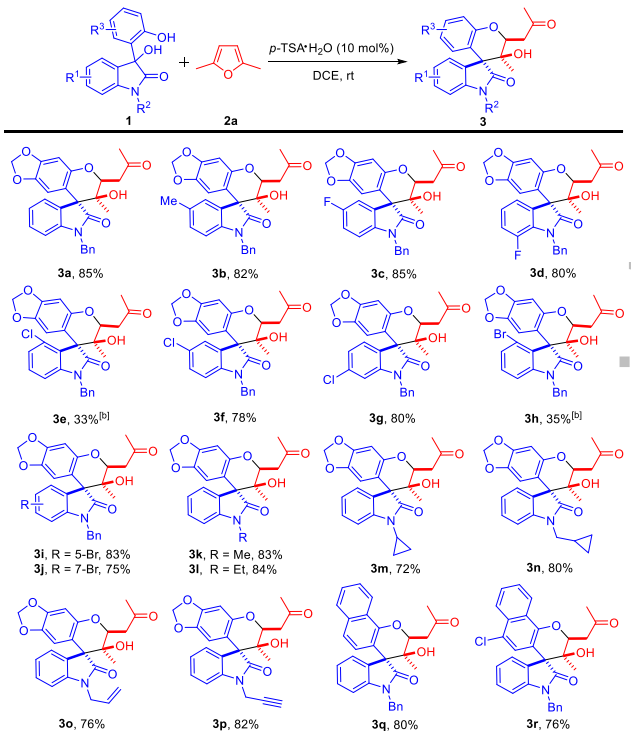


Entry	Catalyst	Solvent	Time	Yield[b] (%)
1	TfOH	DCE	10 s	28
2	*p*-TSA·H_2O	DCE	1 h	82
3	MsOH	DCE	0.1 h	67
4	TFA	DCE	2 d	40
5	(−)-CSA	DCE	1 d	74
6	PA	DCE	2 d	18
7	$PhCO_2H$	DCE	2 d	0
8	AcOH	DCE	2 d	0
9	$Sc(OTf)_3$	DCE	1 h	77
10	$Cu(OTf)_2$	DCE	4 h	0
11[c]	*p*-TSA·H_2O	DCE	2 h	85
12[d]	*p*-TSA·H_2O	DCE	5 h	81
13[c]	*p*-TSA·H_2O	DCM	1.3 h	80
14[c]	*p*-TSA·H_2O	THF	2 d	0
15[c]	*p*-TSA·H_2O	Toluene	5 h	61
16[c]	*p*-TSA·H_2O	MeCN	2 d	27
17[c]	*p*-TSA·H_2O	EtOH	2 d	0
18[c]	*p*-TSA·H_2O	H_2O	2 d	0

[a] Reaction conditions (unless otherwise noted): **1a** (0.1 mmol), **2a** (0.3 mmol), catalyst (20 mol%), solvent (1 mL), room temperature. (−)-CSA = (−)-10-camphorsulfonic acid. PA=1,1'-binaphthyl-2,2'-diyl hydrogen phosphate.
[b] Isolated yield, dr >20:1.
[c] Catalyst (10 mol%).
[d] Catalyst (5 mol%).

dienophiles while oxindole-embedded *o*-QMs served as new four-membered building blocks. However, it is noteworthy that a competitive conjugate addition of electron-rich 2,5-dialkylfurans to *o*-QMs might take place.[7] As a continuation of our research interest in one-step assembly of biological active molecules,[8] herein, we reported an organocatalytic dearomative [4+2] cycloaddition of oxindole-embedded *o*-QMs with 2,5-dialkylfurans, furnishing the pharmaceutically important spiro[chroman-4,3'-oxindole] scaffolds in high yields with excellent diastereoselectivities under mild conditions.

To examine the feasibility of our hypothesis, oxindole-embedded *ortho*-hydroxybenzyl alcohol **1a** and biomass-derived 2,5-dimethylfuran **2a**[9] were selected as model substrates to carry out this reaction (Table 1). To our delight, this reaction proceeded readily with 20 mol% TfOH as a catalyst in DCE at room temperature, furnishing the cycloadduct **3a** in 28% yield with high diastereoselectivity(dr >20:1) (Table 1, entry 1). Afterwards, a series of Brønsted acids and Lewis acids were screened, and it was found that *p*-TSA·H_2O was the optimal catalyst, yielding **3a** in 82% yield (Table 1, entries 2-10). Then the catalyst loading was evaluated, and the yield of **3a** could be increased to 85% when the catalyst loading was decreased to 10 mol% (Table 1, entries 11-12). The final solvent screening implied that DCE was the best solvent for this reaction (Table 1, entries 13-18).



Scheme 2. Substrate scope for dearomative [4+2] cycloaddition of oxindole-embedded *o*-QMs **1** with 2,5-dimethylfuran **2a**. [a] Reaction conditions: **1** (0.1 mmol), **2a** (0.3 mmol), *p*-TSA·H_2O (10 mol%), DCE (1 mL), room temperature. Isolated yields after column chromatography. The dr was determined by ^{1}H NMR analysis, dr >20:1 in all cases. [b] *p*-TSA·H_2O (20 mol%).

With the optimized reaction conditions in hand, the substrate scope was investigated (Scheme 2). Generally, a wide range of oxindole-embedded *ortho*-hydroxybenzyl alcohols **1** with various $R^1/R^2/R^3$ groups proceeded smoothly in this reaction, delivering the corresponding products **3** in high yields with excellent diastereoselectivities (dr >20:1). As for the R^1 groups, both electron-donating and electron-withdrawing substituents were well tolerated and provided products **3a-3j** in high yields. The positions of substituents had trivial impacts on the yields except **3e** and **3h**, the lower yields of which might be attributed to the steric hindrance. Notably, the success of fluorine-substituted products **3c** and **3d** indicated the potential applicability in synthesis of fluorine-containing drugs. With respect to the R^2 groups, in addition to methyl and ethyl groups, cyclopropyl and cyclopropylmethyl substituents with severe ring strain were also compatible with the reaction conditions and gave the desired products in 72%-84% yields (**3k-3n**). Remarkably, substrates bearing dienophilic allyl and propargyl moieties were

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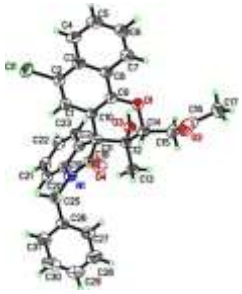
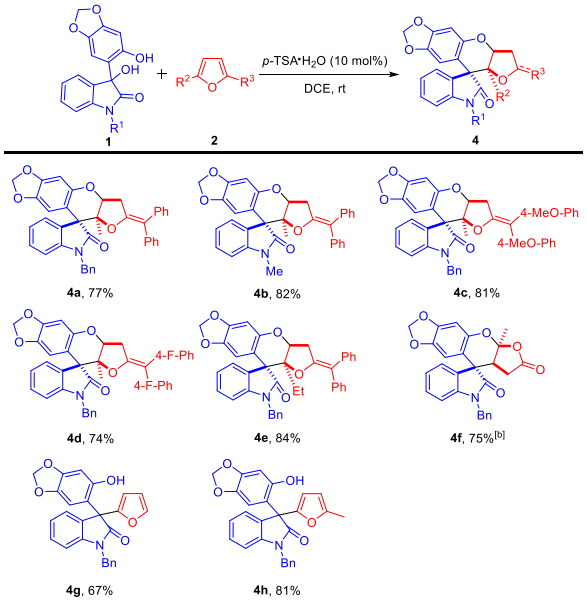


Figure 2. X-ray structure of **3r**.

tolerable as well, exhibiting the excellent selectivity and specificity of this transformation (**3o**-**3p**). Satisfyingly, the oxindole-embedded *ortho*-naphthoquinone methides (*o*-NQMs)[10] also reacted smoothly and afforded products **3q** and **3r** in good yields. The relative configuration of **3r** was unambiguously confirmed by X-ray crystallography (Figure 2).[11]

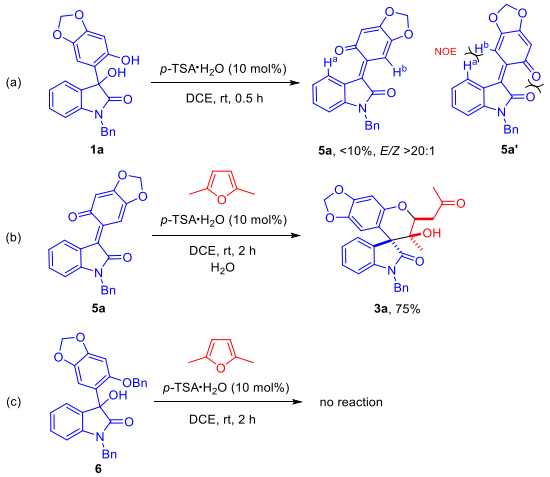
Afterwards, a few other furan derivatives were examined, as shown in Scheme 3. To our delight, the dearomative [4+2] cycloaddition of oxindole-embedded *o*-QMs **1** with various 2-benzhydryl-5-alkylfurans proceeded very well via an IED-HDA



Scheme 3. Substrate scope for dearomative [4+2] cycloaddition of oxindole-embedded *o*-QMs **1** with furan derivatives **2**. [a] Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), *p*-TSA·H_2O (10 mol%), DCE (1 mL), room temperature. Isolated yields after column chromatography. The dr was determined by ^{1}H NMR analysis, dr >20:1 for products **4a**-**4f**. [b] *p*-TSA·H_2O (20 mol%). 5-Methylfuran-2(3H)-one was used.

/tautomerization process, giving the corresponding products **4a**-**e** in 74-84% yields. Moreover, in view of the fact that 5-methylfuran-2(3H)-one could be tautomerized to 5-methylfuran-2-ol under acidic conditions, the reaction with 5-methylfuran-2(3*H*)-one was also performed and the cycloadduct **4f** was provided in 75% yield. It is worth mentioning that the reactivity of 5-methylfuran-2(3*H*)-one serving as a dienophile has never been reported. However, when furan and 2-methylfuran were employed as the reaction partners, the conjugate addition reactions occurred and furnished 3,3-diaryl-substituted oxindoles **4g** and **4h** in good yields.[12]

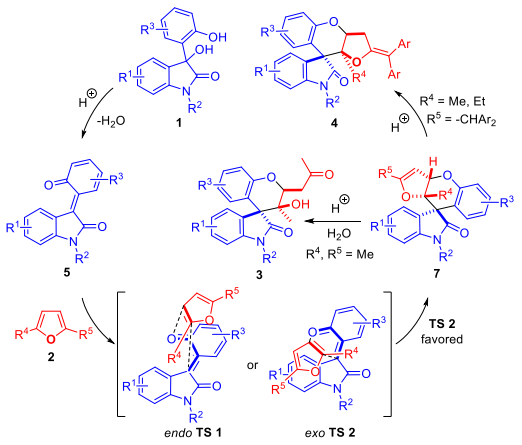
To shed light on the reaction mechanism, several control experiments were performed (Scheme 4). To verify the existence of our proposed oxindole-embedded *o*-QMs, **1a** was subjected to the standard reaction conditions without 2,5-dimethylfuran. We were pleased that the oxindole-embedded *o*-QM intermediate **5a** could be isolated, in a low yield, which might be ascribed to the reversible dehydration and hydrolysis processes (Scheme 4a). There are two possible *E*/*Z* geometric isomers **5a** and **5a'**, and **5a** is much more favored than **5a'** due to the electrostatic interaction and the steric repulsion between O/O atoms. Moreover, failure to observe an NOE signal between H_a and H_b further confirmed the predominance of geometric isomer **5a** (See Supporting Information). When intermediate **5a** was subjected to the reaction conditions with the addition of water, the desired product **3a** was delivered in 75% yield (Scheme 4b). Gratifyingly, other oxindole-embedded *o*-QMs **5b**, **5c** and **5f** could also be isolated and applied to these reactions (See Supporting Information). However, when the hydroxyl group of phenol was protected with a benzyl group, no reaction occurred under the standard reaction conditions, since the generation of oxindole-embedded *o*-QM **5a** was obstructed (Scheme 4c).



Scheme 4. Control experiments.

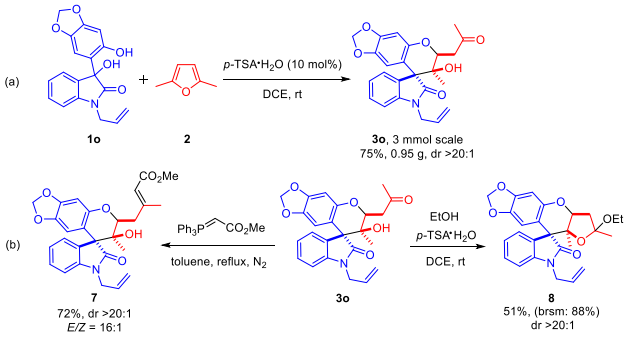
On the basis of the above experiments, a plausible reaction mechanism was proposed (Scheme 5). Initially, the oxindole-embedded *o*-QM intermediate **5** is *in situ* generated *via* the dehydration of **1** in the presence of Brønsted acid, which undergoes subsequent IED−HDA reaction with 2,5-dialkylfuran **2**. In this process, there are two possible transition states *endo* **TS 1** and *exo* **TS 2**. Due to the unique

structure of the oxindole-embedded *o*-QMs, the π-π interaction of the unreacted C=C bond in 2,5-dialkylfuran with the phenyl ring in oxindole unit (**TS 2**) is stronger than that with the diene in sesamol moiety (**TS 1**). Thus the unusual *exo* **TS 2** is much more favored, furnishing the intermediate **7**. When 2,5-dimethylfuran is employed, it undergoes hydrolysis to afford the desired product **3**. On the other hand, the tautomerization of **7** would operate to give product **4** if 2-benzhydryl-5-methylfuran is utilized, which might be ascribed to the formation of more stable conjugate system.



Scheme 5. Proposed mechanism.

To further demonstrate the synthetic utility of this protocol, the scalability of the method was examined, providing **3o** in 75% yield with a maintenance of the excellent diastereoselectivity (Scheme 6a). In addition, a Wittig reaction of **3o** afforded *α*, *β*-unsaturated ester **8** in 72% yield with high *E*/*Z* selectivity, and an interesting ketal product **9** could be obtained in 51% yield with excellent diastereoselectivity when ethanol was added (Scheme 6b).



Scheme 6. Gram-scale synthesis and derivatization of product **3o**.

In conclusion, we have developed an organocatalytic dearomative [4+2] cycloaddition of oxindole-embedded *o*-QMs with 2,5-dialkylfurans, furnishing the biologically important spiro[chroman-4,3'-oxindole] scaffolds in high yields with excellent diastereoselectivities under mild conditions. In this strategy, 2,5-dialkylfurans served as novel dienophiles, and oxindole-embedded *o*-QMs acted as new four-membered building blocks, which will push forwards the chemistry of *o*-QMs in the synthesis of biologically important compounds.

Experimental Section

General Experimental Procedures for the Synthesis of 3 or 4. An oven-dried reaction tube was charged with oxindole-embedded *ortho*-hydroxybenzyl alcohol **1** (1.0 equiv, 0.1 mmol), *p*-TSA·H_2O (10 mol%), DCE (1 mL) and 2,5-dialkylfuran **2** (3.0 equiv, 0.3 mmol). The reaction mixture was stirred vigorously at room temperature and monitored by TLC. After the consumption of **1**, the reaction mixture was directly purified by flash column chromatography (column chromatography eluent, petroleum ether/ethyl acetate) to afford products **3** or **4**.

Acknowledgements

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