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Organocatalytic, Enantioselective, Intramolecular Oxa-Michael Reaction of Alkoxyboronate: A New Strategy for Enantioenriched 1-Substituted 1,3-Dihydroisobenzofurans

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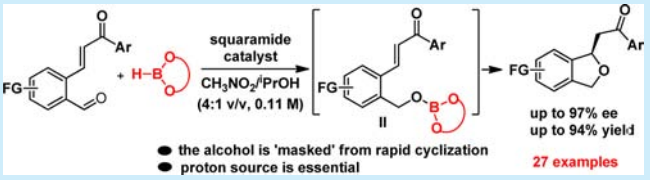
Supporting Information

ABSTRACT: An unprecedented strategy for the synthesis of enantioenriched 1-substituted 1,3-dihydroisobenzofurans via an enantioselective oxa-Michael reaction of *o*-alkoxyboronate containing chalcone (**II**) has been accomplished employing cinchona alkaloid based squaramide bifunctional organocatalyst in the presence of proton source. The corresponding alkoxyboronate intermediates have been readily prepared in situ from *o*-formyl chalcones using neutral borane as hydride source and a tertiary amine moiety which is a counterpart of the catalyst.



Chiral 1-substituted 1,3-dihydroisobenzofurans are important scaffolds that are commonly found in many molecular targets, including the natural product pestacin[1] as well as molecules of fascinating pharmaceutical relevance such as citalopram[2] and synthetic **A** (Figure 1).[3] Despite their importance, to the best of our knowledge, the enantioselective synthesis via catalytic pathways has not been achieved and still remains a major challenge.

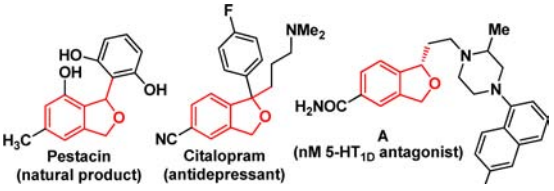
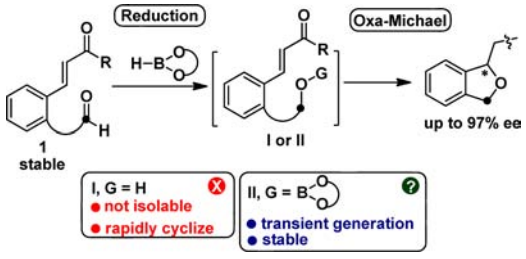


Figure 1. 1-Substituted 1,3-dihydroisobenzofurans structural motif in drugs and natural products.

The oxa-Michael addition reaction is one of the most powerful tools to construct carbon−oxygen bonds.[4] In particular, the intramolecular variants are the most straightforward route to oxoheterocycles. However, the development of asymmetric variants of such an intramolecular oxa-Michael addition still remains significantly challenging because of its rapidity and reversibility.[4b,g] In recent times, chiral bifunctional catalysts have been utilized to surmount such a barrier to achieve highly enantioselective intramolecular oxa-Michael reactions.[5]

Inspired by these elegant reports, we envisaged that enantioenriched 1-substituted 1,3-dihydroisobenzofurans could easily be accessed through an intramolecular asymmetric oxa-Michael reaction of *o*-hydroxymethyl-containing chalcones (**I**) (Scheme 1) using bifunctional catalysts. However, the synthesis of *o*-hydroxymethyl-containing chalcone (**I**, Scheme 1) remained unsuccessful because of its rapid cyclization to the corresponding racemic isobenzofuran (±)-**3e**.[6]

Scheme 1. Strategies for Synthesis of Enantiomerically Enriched 1-Substituted 1,3-Dihydroisobenzofurans



To suppress such rapid cyclization, we hypothesized a transiently generated alkoxyboronate intermediate (**II**, Scheme 1) by which the alcohol counterpart could be potentially masked and would be released only upon further activation. Inspired by the recent success of push/pull-type bifunctional organocatalysis using catalysts bearing a H-bond donor moiety and a tertiary amino group on a chiral scaffold,[7,8] we were interested in pursuing our current interest, the asymmetric intramolecular oxa-Michael addition process of intermediate **II** using such catalysts derived from cinchona alkaloid. We assumed that the tertiary amine part of the catalyst could activate the alkoxyboronate counterpart (the push); on the other hand, the H-bonding counterpart could activate the enone moiety (the pull) (**TS-I**, Scheme 2, second step). Furthermore, such a coordination also preorganized the intermediate to a well-defined orientation, an important prerequisite for asymmetric induction. To achieve the alkoxyboronate intermediate (**II**), the

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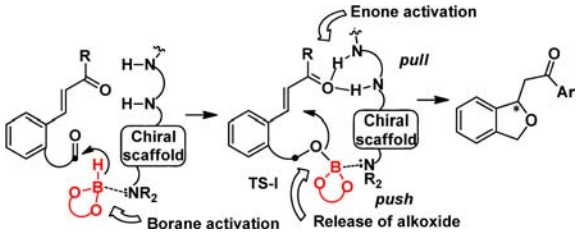
Scheme 2. Concept of the New Catalytic Mode of Action

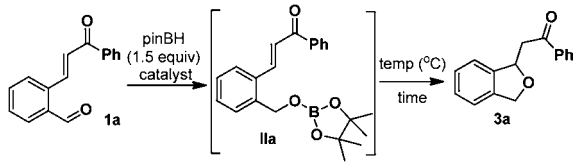


reduction of aldehyde via neutral borane activation catalyzed by tertiary amine (part of the catalyst) has been adopted (Scheme 2, first step).[8]

To materialize this strategy, the reduction of *o*-formyl chalcone **1a** using pinacolborane as hydride source was investigated using 10 mol % of chiral thiourea-based catalyst (**2a**)[9] derived from cinchona alkaloid (Table 1). In anhydrous aprotic solvents such as toluene, EtOAc, $CHCl_3$, CH_2Cl_2, MeCN, and $MeNO_2$, the hydroboration was completed within 45 min to provide the corresponding alkoxyboronate intermediate **IIa**,[10] which was supported by NMR and mass spectroscopic studies, whereas the oxa-Michael addition step of **IIa** remained nearly unachievable in these solvents (entry 1, Table 1). Further, we investigated the feasibility of the reaction in protic solvents (for details, see the Supporting Information).[6] We observed that in case of MeOH, the side reaction to provide the corresponding acetal prohibited the reduction step itself. Interestingly, in EtOH and ^{i}PrOH, although the reduction step remained partially completed (by TLC), the oxa-Michael addition was found to be feasible and provided the desired **3a** with moderate enantioselectivity. The screening of other chiral thiourea (**2a**,**b**)[9] as well as squaramide (**2c**–**f**)[11] catalysts (entry 2–7) in ^{i}PrOH revealed that **2c** is the best catalyst to provide **3a** in terms of high enantioselectivity (91% ee, entry 4). Further, screening of a mixture of ^{i}PrOH and aprotic solvents (1:4 v/v) revealed that a ^{i}PrOH and $MeNO_2$ solvent mixture in 1:4 ratio was the best combination with respect to enantioselectivity (entry 8). To our delight, further increases in the overall reaction yields were observed by increasing the reaction temperature to 45 °C (entry 9) with reduced reaction time. Using H_2O as protic solvent instead of ^{i}PrOH resulted in minor reduction of the enantioselectivity (entry 10). The lowering of the catalyst loading from 10 mol % resulted in decreased reactivity as well as selectivity. The use of only ^{i}PrOH or $MeNO_2$ as solvent at 45 °C was also not effective. Other hydride sources such as $NaBH_4$, $NaB(CN)H_3$, BH_3–SMe_2, and catecholborane were found to be ineffective for such reactions with respect to yields and enantioselectivities.[6]

With the optimized reaction conditions in hand, the scope of the external aryl group has been briefly investigated (Table 2).

Table 1. Optimization of the Reaction Conditions



entry	2	solvent	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	**2a**	aprotic solvents[a]	rt	12	<5	nd
2	**2a**	^{i}PrOH	rt	12	25	81
3	**2b**	^{i}PrOH	rt	12	>5	nd
4	**2c**	^{i}PrOH	rt	12	25	91
5	**2d**	^{i}PrOH	rt	12	39	87
6	**2e**	^{i}PrOH	rt	12	21	81
7	**2f**	^{i}PrOH	rt	12	35	82
8	**2c**	^{i}PrOH/$MeNO_2$[d]	rt	12	77	93
9	**2c**	^{i}PrOH/$MeNO_2$[d]	45	5	100	94
10	**2c**	H_2O/$MeNO_2$[d]	rt	12	100	92

[a]Aprotic solvents such as toluene, EtOAc, $CHCl_3$, CH_2Cl_2, MeCN, and $MeNO_2$. [b]The conversion was calculated based on ^{1}NMR spectroscopy of the crude reaction mixture using anisole as internal standard. [c]Enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. [d]Ratio was 1:4 (v/v).

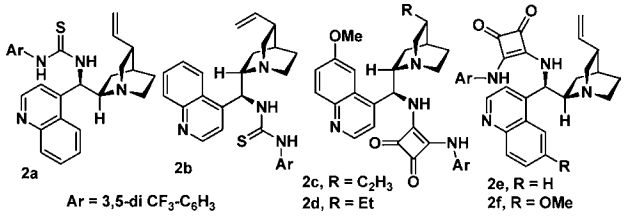
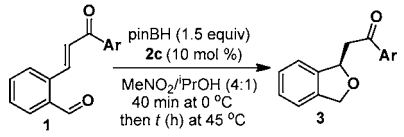
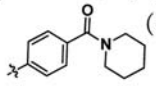


Table 2. Substrate Scope: 1,3-Dihydroisobenzofurans[a]



entry	Ar-, **1**	**3**, *t* (h)	(%)[b]	ee (%)[c]
1	C_6H_5- (**1a**)	**3a**, 4	87	94 (>99)[d]
2	*p*-Me-C_6H_4- (**1b**)	**3b**, 2	82	97
3	*p*-MeO-C_6H_4- (**1c**)	**3c**, 4	89	92
4	*p*-Cl-C_6H_4- (**1d**)	**3d**, 5	85	92 (>99)[d]
5	*p*-Br-C_6H_4- (**1e**)	**3e**, 5	83 (70)[d]	95 (>99)[d]
6	1g scale (**1e**)[e]	**3e**, 12	87 (75)[d]	95 (99)[d]
7	(**1e**)[f]	**3f**, 6	72	90
8	*p*-F-C_6H_4- (**1f**)	**3g**, 5	80	93
9	2,4-diF$_2$-C_6H_3- (**1g**)	**3h**, 6	88	82
10	3,4-diF$_2$-C_6H_3- (**1h**)	**3i**, 4	80	93 (>99)[d]
11	*p*-O_2N-C_6H_4- (**1i**)	**3j**, 3	72 (73)[d]	82 (>99)[d]
12	*p*-F_3C-C_6H_4- (**1j**)	**3k**, 5	76	83 (>99)[d]
13	*p*-EtO_2C-C_6H_4- (**1k**)	**3l**, 8	87	81
14	*p*-NC-C_6H_4- (**1l**)	**3m**, 6	79	83
15	 (**1m**)	**3n**, 6	86	81
16	*p*-Me_2N-C_6H_4- (**1n**)	**3o**, 24	89	82
17	2-Furyl- (**1o**)	**3p**, 2	86	94
18	2-Thyophenyl- (**1p**)	**3q**, 4	98	94
19	1-Naphthyl- (**1q**)	**3r**, 4	40	82

[a]Reaction conditions: **1** (0.225 mmol), pinBH (0.34 mmol, 1.5 equiv), **2c** (0.0225 mmol, 10 mol %) in ^{i}PrOH/CH_3NO_2 (1:4, 0.111 M) at 0 °C for 45 min then 45 °C for 2–6 h. [b]Yields shown are based on isolated products. [c]Enantiomeric excess were determined by HPLC analysis on a chiral stationary phase. [d]The yields and % ee after recrystallization are shown in parentheses. [e]The reduction was carried out at 0 °C for 2 h.. [f]Catalyst **2e** was used instead of **2c**.

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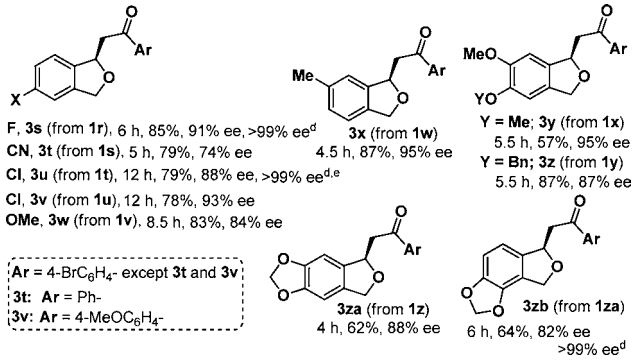
Aryls with electron-withdrawing substituents (F−, di-F−, O_2N−, F_3C−, EtO_2C−, NC−, amide) and electron-donating substituents (Me−, MeO−, Me_2N−) gave the corresponding isobenzofurans **3a−o** in good yields and with high enantioselectivities (81−97% ee). Notably, many of the above-mentioned functional groups such as O_2N−, NC−, ester, amide, and amine, which are generally sensitive toward borane, are found to produce the desired oxa-Michael products under such mild reaction conditions. Heteroaromatics such as 2-furan and 2-thiophene (entries 17 and 18, Table 2) provided high yields and enantioselectivity (94% ee in each case). Furthermore, the use of α-naphthyl ring resulted in decreased yield and enantioselectivity (entry 19). Interestingly, most of these products are crystalline compounds; optically pure products (>99% ee) could be obtained after recrystallization (entries 1, 4, 5, and 10−12). In addition, when the reaction of **1e** was scaled 14-fold (1g, 3.2 mmol) with similar catalyst loading under similar reaction conditions, even better results were obtained (entry 6). Moreover, the optical antipode (for example, **3f** instead of **3e**, entry 7) could also be obtained with high enantioselectivity using catalyst **2e** instead of **2c**.

To expand the substrate scope, our further examination focused on the substitution of the internal aryl group (summarized in Scheme 3). Good yields and high enantioselectivities were achieved in the reductive oxa-Michael addition of a variety of substituted *o*-formyl chalcones (**1r−za**). The presence of either electron-donating or electron-withdrawing substituents on the internal aryl moiety (**3s−zb**) were found to be equally effective. In the cases of **3zb** and **3t**, reduced enantioselectivity (82% and 74% ee, respectively) was observed. Notably, compounds **3u**,**v** are synthetic precursors for several 5HT receptor agonists (**A**, in Figure 1).[3]

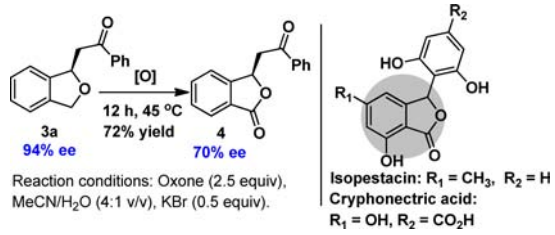
Inspired by the importance of the 1-substituted phthalide (isobenzofuran-1(3*H*)-ones) moiety in natural products such as isopestacin and cryphonectric acid possessing significant biological activities,[12] we intended to convert our synthesized chiral substituted isobenzofurans to the phthalide moiety by benzylic oxidation as shown in Scheme 4. A decrease in enantioselectivity was observed, probably due to the reversible oxa-Michael addition of **3a** under basic conditions as well as the formation of a benzylic radical under such oxidation conditions.[13]

Scheme 3. Substrate Scope: 1-Substituted 1,3-Dihydroisobenzofurans[a−c]



[a]The reaction conditions were same as those in Table 2. [b]Isolated yield. [c]Enantiomeric excess were determined by HPLC analysis on a chiral stationary phase. [d]After recrystallization. [e]For absolute configuration, see the literature value (ref 3).

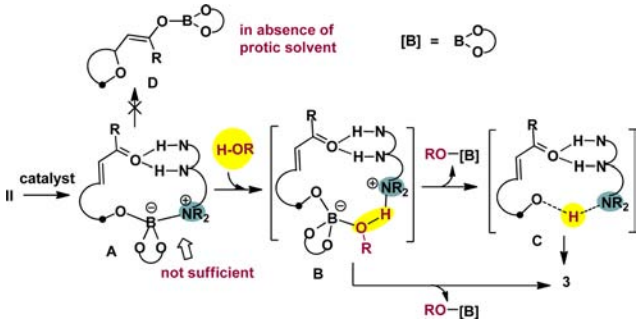
Scheme 4. Benzylic Oxidation of Chiral 1-Substituted Isobenzofurans to 1-Substituted Phthalide



The quantitative kinetic isotopic effect (KIE, $k_H/k_D = 3.84$) for *ortho*-cyclization of alkoxyboronate was also calculated on the basis of ^{1}H NMR studies in the presence of H_2O and D_2O.[6] This indicates the crucial role of the proton source in the rate-determining step.

On the basis of the above observations, a plausible mechanism for the oxa-Michael addition of alkoxyboronate **II** is depicted in Scheme 5.[14] In the absence of a protic solvent, the catalyst alone may not be able to push the oxa-Michael addition to occur to provide the intermediate **D**.[15,16] In the presence of a protic solvent, the decomposition of the alkoxyboronate to corresponding alcohol **C**, via intermediate **B**, followed by alcohol cyclization could occur to provide the desired product **3**. An alternative pathway in which the direct cyclization of the intermediate **B** could also be possible. However, such requirement of an alcohol in addition to a Lewis base catalyst have already been realized for the activation of diborane.[17]

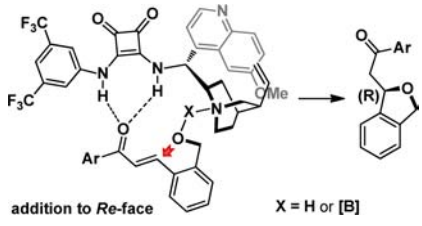
Scheme 5. Proposed Mechanism



A transition state similar to those previously proposed for the squaramide/thiourea catalysts in the oxa-Michael reaction of enone[7,8] may be invoked to explain the observed absolute stereochemistry of product (Scheme 6).

In summary, a highly enantioselective intramolecular oxa-Michael reaction of alkoxyboronate has been achieved employing a chiral bifunctional organocatalyst. Alkoxyboronates are generated in situ by the reduction of corresponding aldehyde

Scheme 6. Proposed Model for the Enantioselectivity-Determining Step



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using neutral borane as hydride source in the presence of the catalyst. The current methodology leads to highly enantioselective synthesis of 1-substituted 1,3-dihydroisobenzofurans with a broad substrate scope. Further studies to clearly understand the reaction mechanism and further synthetic applications are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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