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# A Highly Efficient Chirality Switchable Synthesis of Dihydropyran-Fused Benzofurans by Fine-Tuning the Phenolic Proton of β-Isocupreidine (β-ICD) Catalyst with Methyl

Feng Wang, Chen Yang, Xiao-Song Xue, Xin Li,* and Jin-Pei Cheng*[a]

**Abstract:** A highly enantioselective β-isocupreidine (β-ICD) catalyzed synthesis of dihydropyran-fused benzofurans through [4+2] cycloaddition of allenoates and benzofuranone alkenes was developed. Switchable chirality inversion of cycloaddition products was achieved by replacing the phenolic proton of the catalyst with a methyl, demonstrating an amazing effect of minimal structural variation on inverting enantioselectivity. DFT calculations were utilized to elucidate the origin of the observed phenomena. Computation also provided a clue for a rational design in which the multi-hydrogen bond with the alcohol additive was found to improve the enantioselectivity of the cycloaddition. Finally, the substrate scope was examined, in which a number of functionalized dihydropyran-fused benzofurans could be obtained in high yields (up to 97%) with very good regio- (>20:1) and enantioselectivities (up to 98:2 e.r.).

## Introduction

Stereoselective catalysis has long been an attractive topic in synthetic chemistry. One of the significant endeavors is to pursue both *R/S* enantiomers with high enantiopurity. To realize it, a general strategy using the same starting material, catalyst, or ligand with opposite configurations is usually applied. This approach has some limitations, however, when the corresponding catalysts or ligands of reversed chiral configuration are difficult to achieve. More recently, inversed enantioselectivity has also been found in a number of studies in which quite diverse catalytic strategies were utilized, such as by changing the additives, temperature, solvent combination, manner of adding reactants, or by minor modifications of catalyst or ligand.[1,2]

While the outcomes of all the above are highly remarkable, in the present study of the chiral synthesis of dihydropyran-fused benzofurans by cycloaddition of allenoates and benzofuranone alkenes, we have discovered an unexpected enantioselectivity switchable catalysis using β-ICD and methylated β-ICD as the respective catalysts. As shown in Figure 1, the *R* enantiomer was derived by using the normal β-ICD as catalyst, whereas a very small change on β-ICD, just by replacing its phenolic proton with methyl, resulted in an *S* isomer as the primary product. The β-isocupreidine (β-ICD),[3] which is known as a typical cinchona alkaloid type organocatalyst,[4,5] has been explored intensely in a number of important asymmetric transformations.[6–8] To obtain the products of opposite absolute configurations with this favorable catalyst, in previous works,[9] enantiocomplementary catalysts of β-ICD had to be designed and synthesized, which, however, required lengthy transformations and sometimes harsh reaction conditions. Thus, new strategies and/or new catalyst design approaches to achieve opposite absolute configurations remain as a formidable challenge and hence are still highly desirable.

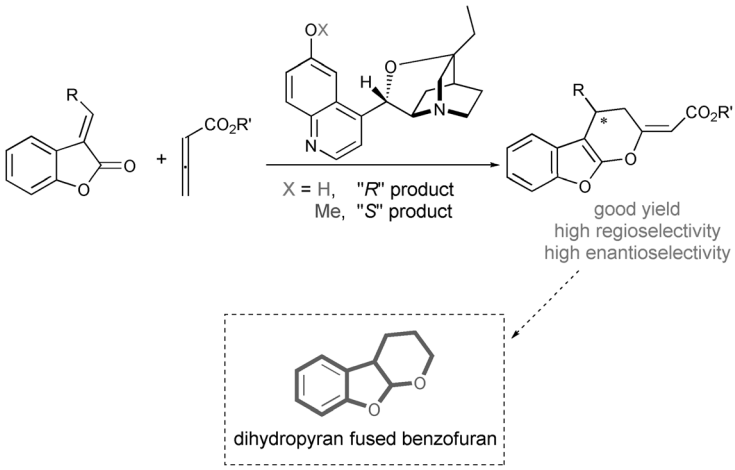


**Figure 1.** Enantiodivergent [4+2] cycloadditions of benzofuranone alkenes with allenoates.

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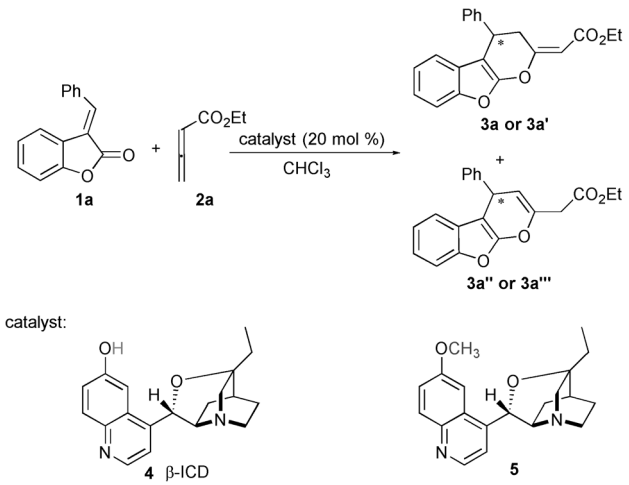
It is noteworthy that, although the cinchona alkaloid type Lewis base catalyzed enantioselective cycloadditions have already been investigated,[7,8,10] to our knowledge, the stereoadjustable inversion with β-ICD catalytic system for cycloaddition reactions has not been reported yet. In addition, the present study discloses a new insight into the strategy to induce enantiomers inversion with the cinchona alkaloid catalytic system. Besides, since the targeted dihydropyran-fused benzofuran itself represents a privileged scaffold in many natural products that exhibit a range of biological activities,[11] the present method should be of an added value for obtaining chiral dihydropyran-fused benzofuran compounds with the desired high *R* or *S* enantiopurity.

## Results and Discussion

The intent of the current study was for an organocatalytic synthesis of chiral dihydropyran-fused benzofuran derivatives. Initially, we focused on the β-ICD-catalyzed reaction between (*E*)-3-(benzylidene)benzofuran-2-one (**1a**) and ethylallenoate (**2a**). To our delight, cycloaddition product **3a** was obtained with good yield and regioselectivity with moderate enantioselectivity (90% yield and 87:13 e.r., Table 1). To our surprise, however, when using catalyst **5**, in which the phenolic hydroxyl group was protected by a methyl group, the opposite absolute configuration product **3a**′ was obtained in 92% yield and with 15:85 e.r. (Table 1).[12] Further lowering down the reaction temperature was found to significantly increase both the regio- and enantioselectivity.[13]

**Table 1.** Initial screening.[a]




| *T* [°C] | *t* [h] | Yield [%] | Product ratio |
|---|---|---|---|
| 20 | 48 | 90 | **3a**/**3a**″ = 9:1, 87:13 e.r. |
| −30 | 96 | 88 | **3a**/**3a**″ = > 20:1, 94:6 e.r. |
| 20 | 12 | 92 | **3a**′/**3a**″ = > 20:1, 15:85 e.r. |
| −30 | 24 | 90 | **3a**′/**3a**″ = 20:1, 11:89 e.r. |

[a] Reactions were conducted with 0.1 mmol **1a**, 0.15 mmol **2a**, and 20 mol% catalyst in 0.5 mL $CHCl_3$; isolated yields (regioselectivities were determined by $^1H$ NMR spectroscopic analysis of crude products); e.r. values were determined by chiral HPLC analysis.

To understand these intriguing observations, DFT calculations were conducted to elucidate the cause of the enantioselective inversion between catalyst β-ICD and **5**.[14–16] Given the fact that the methylene moiety in methyl allenoate can be *syn* or *anti* to the quinoline moiety of β-ICD/**5** in the enantiocontrolling C–C bond formation step, four possible transition states were considered in the present study (Figures 2 and 3).

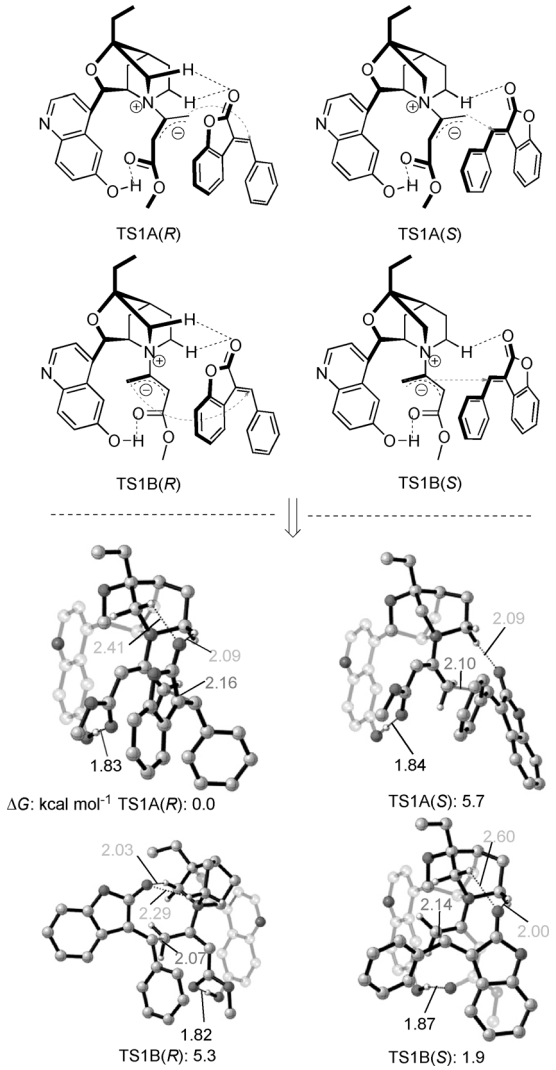



**Figure 2.** Optimized structures of key transition states for asymmetric induction by β-ICD. Most hydrogen atoms have been removed for clarity. Dark grey numbers indicate the carbon–carbon bond-forming distances [Å]; light grey numbers indicate the ($N^{\delta+}$)C–H···O distances [Å]; black numbers indicate the O–H···O distances [Å].

Truhlar's M06L functional[17] in conjunction with the standard 6-31G(d) basis set was used for optimization of the geometry of all transition states (**TS**). As the B97-D functional[18] has been shown to be capable of providing accurate reaction barriers while also reliably describing the noncovalent interactions present in transition states, single-point energy calculations were performed at the B97-D/6-311+G(d, p) level with the M06L/6-31G(d) structures. The new SMD solvation model was

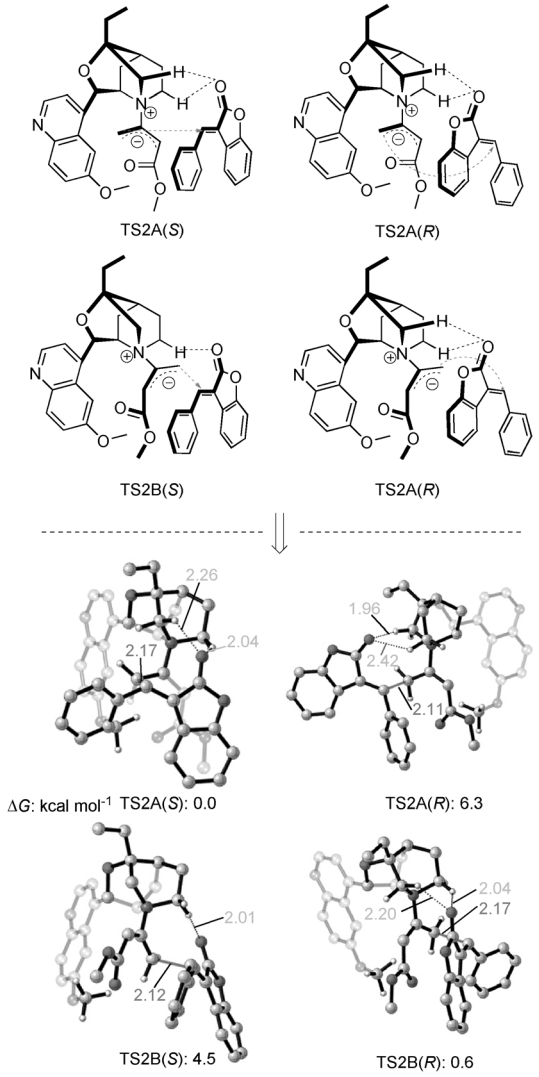



**Figure 3.** Optimized structures of key transition states for asymmetric induction by catalyst **5**. Most hydrogen atoms have been removed for clarity. Dark grey numbers indicate the carbon–carbon bond-forming distances [Å]; light grey numbers indicate the $(N^{\delta+})C–H\cdots O$ distances [Å].

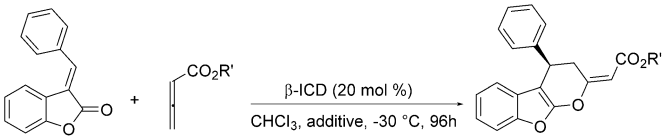
used to account for the effects of the chloroform environment.[19] All calculations were carried out with the Gaussian 09 packages.[20] All energetics reported throughout the text are in kcal mol$^{-1}$ and the bond lengths are in angstroms (Å). Structures were generated using CYLview.[21]

The calculation demonstrates that the most stable transition-state structure, namely TS1A(R) (Figure 2), of the β-ICD-induced reaction leads to the "*R*" product with the computational predicted e.r. value of 98:2 (1.9 kcal mol$^{-1}$), which is in good agreement with the experimental value 95:5.[14] In TS1A(R), the OH of β-ICD forms a relatively strong hydrogen bond with the carbonyl oxygen of allenoate as indicated by the short hydrogen bond distance (O–H···O: 1.83 Å), and the methylene moiety of methyl allenoate is *anti* to the quinoline moiety of β-ICD. Moreover, the nonconventional $(N^{\delta+})C–H\cdots O$ interactions between the C–H moiety of β-ICD quinuclidine and the carbonyl oxygen atom of benzofuranone may also contribute to the stabilization of TS1A(R).[22] Inspection of TS1A(R) and TS1B(S) shows that the O–H···O distance in the latter is 0.04 Å longer than that in the former. This indicates that the O–H···O hydrogen-bonding interaction in TS1B(S) should be weaker than that in TS1A(R), which is supposed to be a key factor that contributes to the energy difference between TS1A(R) and TS1B(S).

When the OH group of β-ICD is methylated (Figure 3), the key factor (O–H···O interaction) that is capable of stabilizing the "*R*" transition-state of a β-ICD-catalyzed reaction is lost. In contrast, the $(N^{\delta+})C–H\cdots O$ interactions between the C–H moiety of quinuclidine in **5** and the carbonyl oxygen of benzofuranone in the four transition states should all be strengthened relative to the corresponding interactions of the transition states in Figure 2 (or Figure 3), which can be manifested by comparing the bond distances. The enhancement of the C–H···O interactions in TS2A(S) is larger than the corresponding interaction in TS2B(R). The above two points likely result in the alternation in the most favorable transition state when the catalyst is changed from β-ICD to **5**. The calculation demonstrated that the TS2A(S) becomes the most stable transition state for the **5**-catalyzed cycloaddition, yielding an "*S*" product with the computational predicted e.r. value of 22:78 (0.6 kcal mol$^{-1}$), which corresponds quite well with the experimental value 13:87.[14]

The DFT calculations confirmed that the phenolic hydroxyl group of β-ICD, which is involved in activation of the carbonyl oxygen of allenoate through O–H hydrogen bond, should be a key element to stabilize the transition state. Following this line, it is reasonable to wonder if multi-hydrogen bonding could enhance stabilization of the transition states so as to affect the stereocontrol. To test this, some additives, such as hydrogen-bond donor compounds, may be thought as candidates to improve the stereocontrol of the reaction. We then examined a range of alcohols as additives in this [4+2] cycloaddition. Encouragingly, alcohol additives were indeed found to improve the e.r. values of the cyclization products (Table 2). As shown in Figure 4, correlation of the log(e.r.) values with

**Table 2.** Optimization of additives.[a]




**1a** **2** **3a** or **6**

| Entry | Additive | R′ | Yield [%][b] | e.r.[c] |
|---|---|---|---|---|
| 1 | – | **2a**: Et | **3a**: 88 | 94:6 |
| 2 | EtOH | **2a**: Et | **3a**: 90 | 96:4 |
| 3 | MeOH | **2a**: Et | **3a**: 60 | 97:3 |
| 4 | *i*PrOH | **2a**: Et | **3a**: 75 | 95:5 |
| 5 | *t*BuOH | **2a**: Et | **3a**: 71 | 94:6 |
| 6 | MeOH | **2b**: Me | **6a**: 91 | 98:2 |

[a] Reactions were conducted with 0.1 mmol **1a**, 0.15 mmol **2**, and 20 mol% β-ICD with 0.1 mmol additive in 0.5 mL $CHCl_3$ at −30 °C. [b] Isolated yields (regioselectivities >20:1, determined by $^1$H NMR spectroscopic analysis of crude products). [c] Determined by chiral HPLC analysis.

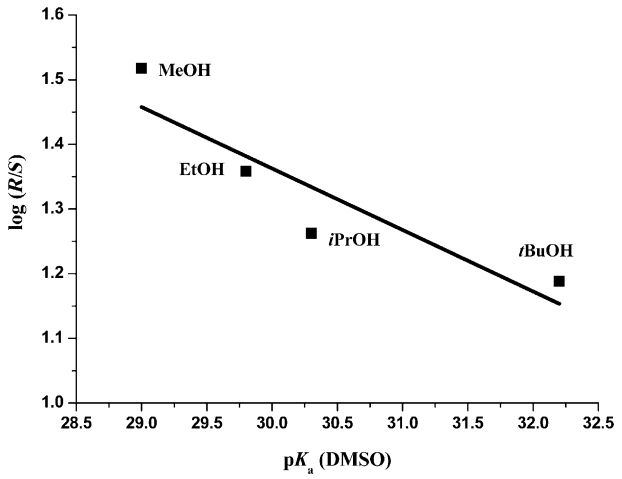



**Figure 4.** Correlation between the logarithms of the product e.r. values and p$K_a$s of the corresponding alcohols.

the p$K_a$s of the corresponding alcohols followed a basically linear pattern, which indicated that a better proton-releasing alcohol favors higher enantioselectivity.[23] This further implies that the proton-donating ability of the additive is associated with hydrogen-bond strengthening. The relatively lower yield observed with methanol as an additive (Table 2, entry 3) may be attributed to a possible ester exchange between the additive and the allenoate ester. To overcome this problem, methyl allenoate was joined with methanol as the additive. As anticipated, the isolated yield of **6a** indeed rose to 91% with a further increase of the e.r. value to 98:2 (entry 6).

It is worth mentioning that the known examples for alcohol as a hydrogen-bonding donor to participate in the stereocontrol in an organocatalytic system is very rare.[24] In order to find out the reason, a kinetic study was conducted. As seen in Figure 5, the observed kinetic isotope effect ($k_H/k_D = 1.73$) of the additive (methanol/[$D_4$]methanol) suggests that the added alcohol have indeed taken a part in the stereocontrol process.[25] Theoretical calculations provide further support to this point. As shown in Figure 6, the methanol-bridged transition states that may account for the enantioselectivity increase were proposed. Compared to the situation in Figure 2 in which the TS1A(R) is directly stabilized by C-6′—OH of β-ICD (1.83 Å, Figure 2), the methanol-relay hydrogen bond in the TS3A(R) of Figure 6 appeared to be shorter (1.71 Å) and thus would make the allenoate intermediate more stable. A close scrutiny into the transition structures TS3A(R) and TS3B(S) reveals that the methanol-relay hydrogen bonds in TS3A(R) (1.68 and 1.71 Å) are stronger than that in TS3B(S) (1.72 and 1.76 Å). Additionally, TS3A(R) should be better stabilized by another methanol than TS3B(S) through hydrogen-bonding interactions (1.80 Å in TS3A(R) vs. 1.85 Å in TS3B(S) in Figure 6). Consequently, TS3A(R) becomes even more stable than TS3B(S) by 2.5 kcal mol$^{-1}$, which leads to a higher enantioselectivity (e.r. value of 99.4:0.6) in the presence of methanol. This calculation result is in good agreement with the experimental e.r. value of 98:2 (entry 6 in Table 2). Clearly, the calculation can well reproduce the experimentally observed increased enantioselectivity.

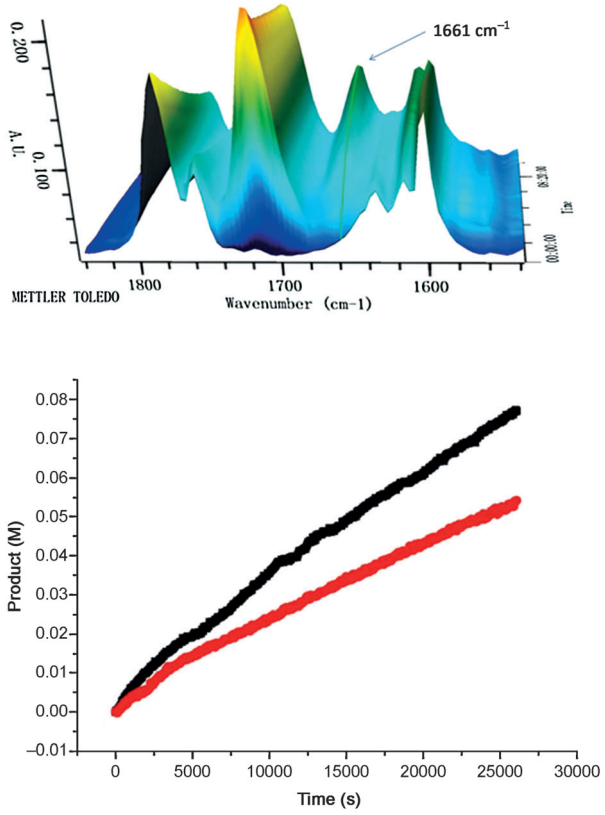



**Figure 5.** a) 3D stack plot of spectra obtained by FTIR spectroscopy; b) representative product *t* plot to determine the initial reaction rate. ■: MeOH; ●: [$D_4$]MeOH.

Next, the substrate scope of the present [4+2] cycloaddition reaction was also examined (Table 3). The reactions proceeded well with a range of 3-subsituted aryl vinyl benzofuran-2-ones bearing either electron-withdrawing or -donating substituents. In most cases, the corresponding products were obtained in good to high yields (71–92%) with very good enantioselectivities (up to 98:2 e.r.). It was noted that the reactivity and enantioselectivity of the reaction are sensitive to the substitution position of the aryl group. Relatively lower yield and enantioselectivity were obtained when *o*-substituted aryl vinyl benzofuran-2-one was the substrate (Table 3, **6n**). The reaction of substrate with larger aromatic ring, such as 2-naphthyl, also gave the corresponding product with good yield and excellent enantioselectivity (Table 3, **6o**).

We further surveyed several 3-subsituted vinyl benzofuran-2-ones in the [4+2] cycloaddition catalyzed by **5**, in which benzyl allenoate was screened as the optimal allenic ester.[26] The reactions were generally conducted at −30 °C for 20–96 h. A variety of 3-subsituted aryl vinyl benzofuran-2-ones with either electron-withdrawing or -donating groups could be tolerated, affording the expected chiral dihydropyran-fused benzofurans derivatives in good yields with good enantioselectivities (Table 4). Furthermore, 3-substituted heterocyclic vinyl benzofuran-2-ones also showed good activities, in which the [4+2] cycloaddition products were obtained with very good enantioselectivities (Table 4, **7p**′ and **7q**′). It is noteworthy that

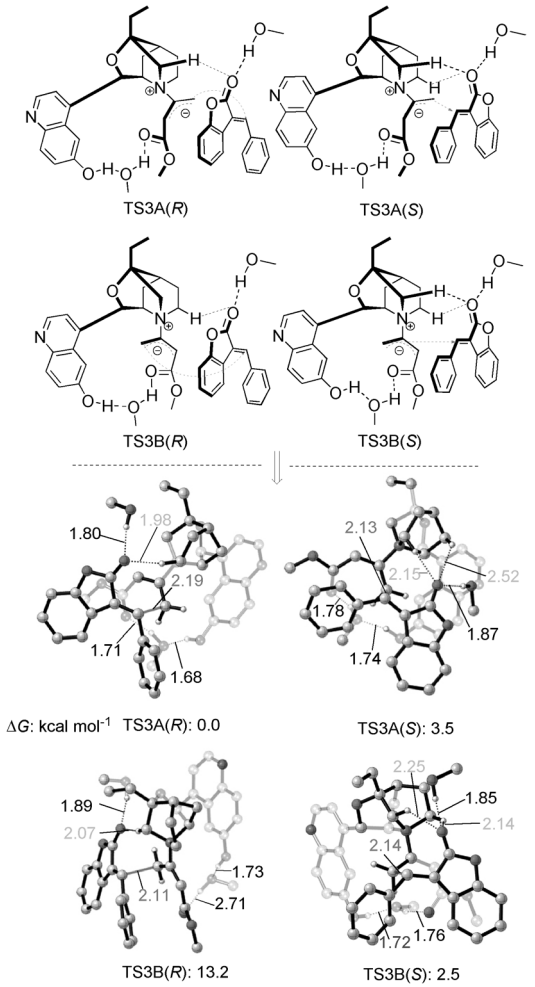
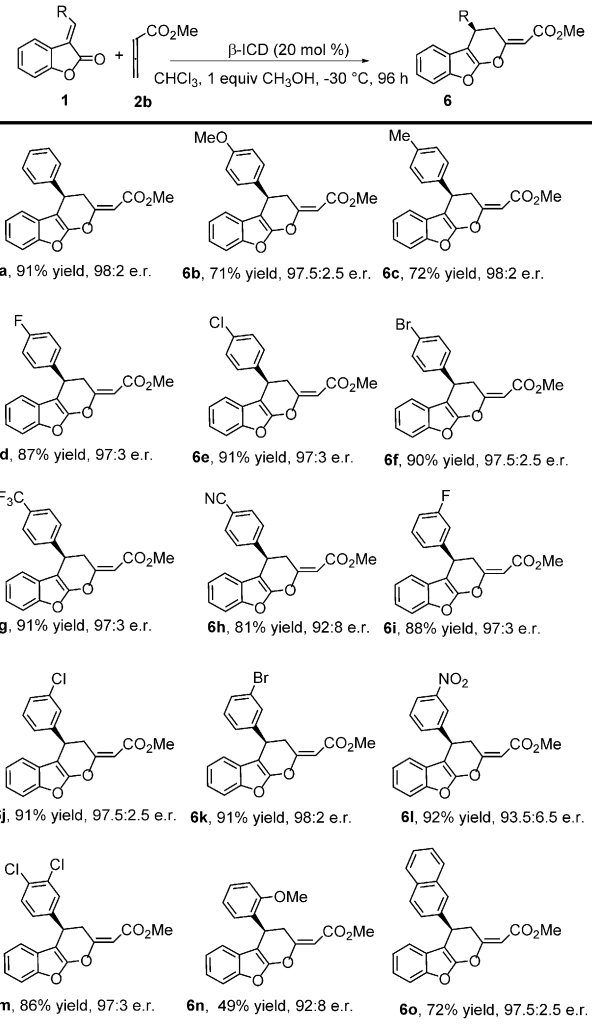



**Figure 6.** Optimized structures of key transition states for asymmetric induction by β-ICD with methanol as additive. Most hydrogen atoms have been removed for clarity. Dark grey numbers indicate the carbon–carbon bond-forming distances [Å]; light grey numbers indicate the ($N^{\delta+}$)C–H···O distances [Å]; black numbers indicate the methanol-relay hydrogen-bond distances [Å].

**Table 3.** Substrates scope catalyzed by β-ICD.[a]




[a] Conditions: reactions were performed with 0.1 mmol **1**, 0.15 mmol **2b**, and 20 mol% β-ICD in 0.5 mL $CHCl_3$ with 1 equiv MeOH at −30 °C (regioselectivities >20:1, by $^1$H NMR spectroscopic analysis of the crude products); isolated yield; e.r. values were determined by chiral HPLC analysis.

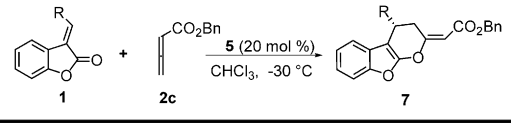
the inversion of enantioselectivity was obtained for all the examined examples, when the reactions were catalyzed by β-ICD (Table 4, e.r. values in parentheses).

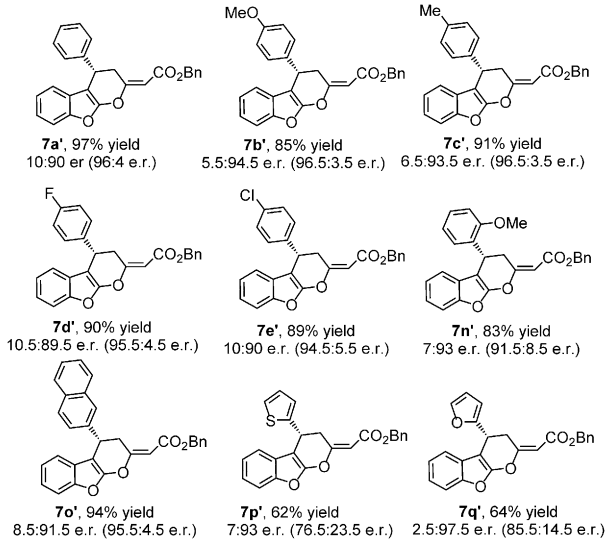
To demonstrate the potential of the current strategy in the context of chiral synthesis, a series of conversions of product **3a** were carried out. As shown in Figure 7, compound **3a** can be easily reduced to **8** by diisobutylaluminium hydride (DIBAL-H) in high yield and retentive enantioselectivity. Subsequent Mitsunobu reaction between **8** and 4-chloro-3,5-dimethylphenol afforded ether **9** in good yield albeit with a slightly lower e.r. value.

## Conclusion

In summary, we have developed the first examples of the enantioselective [4+2] cycloadditions of allenoates with benzofuranone-type electron-deficient alkenes through β-ICD catalysis. The reaction scope is substantial, and a number of functionalized dihydropyran-fused benzofurans could be obtained in high yields with very good regio- and enantioselectivities. A noteworthy switchable chirality inversion of cycloaddition products was achieved by replacing the phenolic proton of the catalyst with a methyl, demonstrating an amazing effect of minimal structural variation on inverting enantioselectivity. DFT calculations were conducted to elucidate the origin of the observed chirality inversion and to provide a clue for a rational design strategy to achieve enhanced levels of enantioselectivity by participating of methanol as additive in the reaction. Further DFT calculations showed that alcohol additives functioned as hydrogen-bonding donors to participate in the formation of multiple hydrogen-bonding catalytic systems, which stabilized the transition state of the stereocontrol step. It is believed that this study disclosed a new insight into the strategy to induce enantiomers inversion with the cinchona alkaloid catalytic system.

**Table 4.** Substrates scope catalyzed by catalyst **5**.[a]




[a] Conditions: reactions were performed with 0.1 mmol **1**, 0.15 mmol benzyl allenoate, and 20 mol% **5** in 0.5 mL $CHCl_3$ at −30 °C (regioselectivities > 20:1, by $^1$H NMR spectroscopic analysis of crude products); isolated yield; e.r. values were determined by chiral HPLC analysis; the e.r. in parentheses were the results catalyzed by β-ICD under identical conditions.

## Experimental Section

### General procedure for the synthesis of the [4+2] cycloaddition product (3a as an example)

Methanol (0.1 mmol) and ethyl allenoate **2a** (0.15 mmol, 1.5 equiv) were added to a stirred solution of (*E*)-3-(benzylidene)benzofuran-2-one (**1a**) (0.1 mmol) and β-ICD (0.02 mmol) in dry $CHCl_3$ (0.5 mL) under −30 °C. The reactions were monitored by TLC analysis. After **1a** was consumed, the reaction solution was concentrated in vacuo and the crude was purified by flash chromatography to afford the product. The regioselectivity was determined by $^1$H NMR spectroscopy of the crude product. The e.r. value was determined by chiral HPLC analysis. For complete experimental details and characterization of compounds, see the Supporting Information.

## *Acknowledgements*

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**Keywords:** chirality inversion · cycloadditions · density functional calculations · Lewis base · switchable enantioselectivity

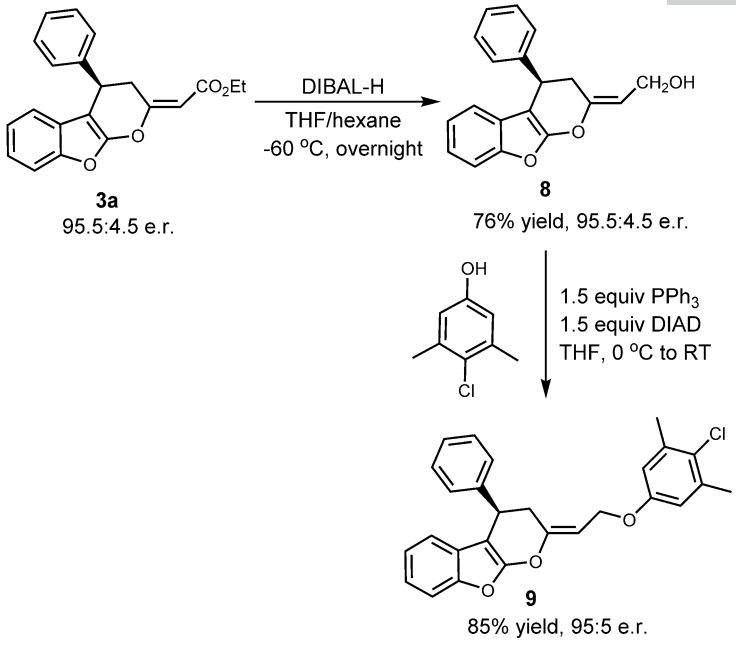


**Figure 7.** Product transformation. DIAD = diisopropyl azodicarboxylate.

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[25] For details of the KIE experiment, see the Supporting Information.

[26] For details of the screening result, see the Supporting Information.

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# FULL PAPER

**Organic Chemistry**

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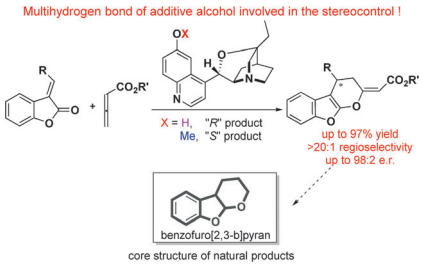
## A Highly Efficient Chirality Switchable Synthesis of Dihydropyran-Fused Benzofurans by Fine-Tuning the Phenolic Proton of β-Isocupreidine (β-ICD) Catalyst with Methyl




**Enantioselectivity inversion**: Highly enantioselective β-isocupreidine (β-ICD)-catalyzed [4+2] cycloadditions of allenoates and benzofuranone-type electron-deficient alkenes have been developed. Switchable enantioselectivity of the cycloaddition products were obtained when the methylated catalyst was used. DFT calculations were conducted to explain the selective inversion (see scheme).