

Chiral Calcium Phosphate Catalyzed Enantioselective Amination of 3-Aryl-2-benzofuranones

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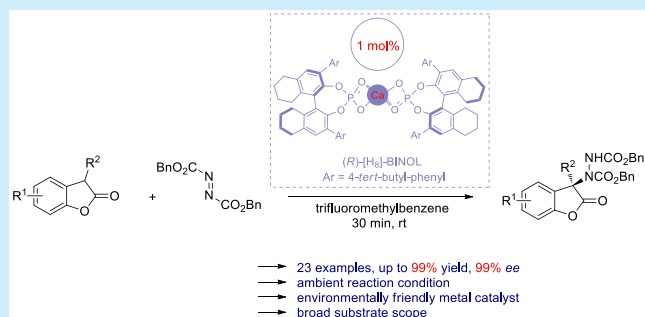


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Supporting Information

ABSTRACT: A 4-*tert*-butyl-phenyl substituted (*R*)-[H₈]-BINOL chiral calcium phosphate catalyzed enantioselective amination of 3-aryl-2-benzofuranones with dibenzyl azodicarboxylate is described. The catalyst loading of the reaction is 1 mol %. This transformation is facile and has a high degree atom economy, which gave products with good yields and high enantioselectivities (79% to 99%). This reaction has excellent *ee* and a broad substrate scope with mild reaction conditions.



Enantioselective C–N bond formation at the α -position of carbonyl compounds is an important transformation. Chiral α -amino carbonyl compounds are present in numerous natural products. There are several novel enantioselective amination reactions that include aldehydes,¹ ketones,² 1,3-dicarbonyls,³ 2-oxindoles,⁴ and α -cyanoacetates,⁵ which could produce chiral α -amino carbonyl compounds.

Asymmetric amination at the α -position of 2-benzofuranones generates chiral 3-amino-2-benzofuranones which are present in medicinally valuable products like (–) fumimycin⁶ (antibacterial), sorbicillactone A⁷ (antileukemic), hopeahainol A⁸ (acetylcholinesterase inhibitor), and phalarine⁹ (Figure 1). Over the past decades, there are only two examples of asymmetric amination of 2-benzofuranones;¹⁰ however, they

exhibit a narrow substrate scope, require long reaction times and need a comparatively higher catalyst loading. Therefore, developing an efficient method for the amination of 3-aryl-2-benzofuranones is desirable. Furthermore, in the field of phosphoric acid catalysis, the activation of 2-benzofuranones appears to be only disclosed by Ooi and co-workers¹¹ using transition-metal Pd catalysis, by taking advantage of the structural modularity of ion-paired chiral ligands. The development of highly efficient CPA-activation of 2-benzofuranones is a challenge to organic chemists. Here we reported the amination of 3-aryl-2-benzofuranones using a chiral calcium phosphate.

Since chiral phosphoric acids (CPAs) were introduced to asymmetric catalysis in 2004,¹² they have been applied in various enantioselective reactions.¹³ Successful efforts were also made to increase the acid strength (low *pK_a*) in order to enable additional catalysis to be achieved.¹⁴ In 2010, a significant breakthrough in this field was made by Ishihara and co-workers. He found that calcium phosphate could be used as a catalyst to achieve a highly enantioselective Mannich-type reaction of aldimines with 1,3-dicarbonyl compounds.¹⁵ This report paved the way for the extensive use of chiral metal phosphates as a catalyst for additional asymmetric organic transformations.¹⁶

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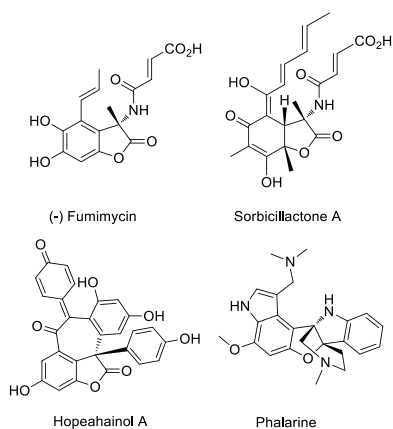


Figure 1. Some important medicinal chiral 2-benzofuranones.

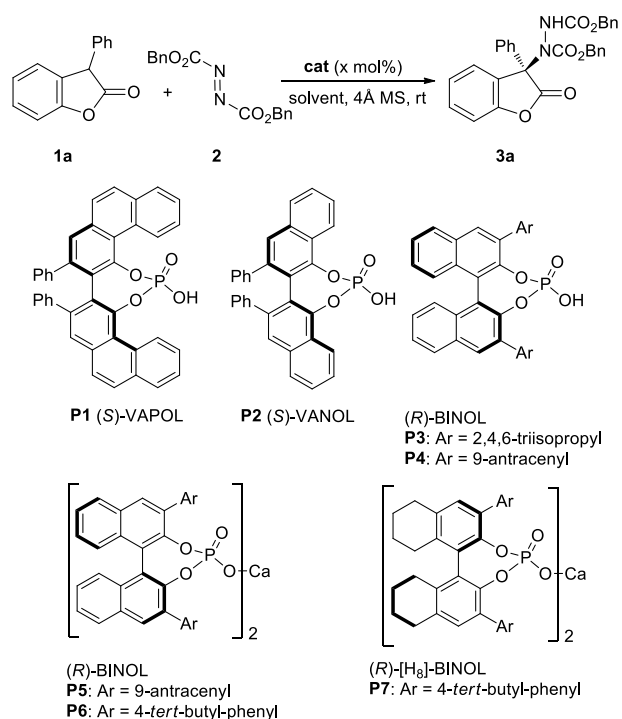
Calcium phosphates are excellent asymmetric catalysts among the various alkali metal phosphates and alkaline-earth metal phosphates. In the past decade, chiral calcium phosphate developed rapidly,¹⁷ successfully catalyzing benzoyloxylation^{17a} and chlorination^{17b,c} of 3-aryloxindoles, hetero-Diels–Alder reactions,^{17d,e} Mannich reactions of cyclic 1,3-diketones,^{17f} imide addition of imines,^{17g} amination of enamides,^{17h} and chloroamination of enecarbamates.¹⁷ⁱ

In 2011, our group reported a highly enantioselective catalytic benzoyloxylation of 3-aryloxindoles catalyzed by calcium phosphate.^{17a} In the same year, our group disclosed a highly enantioselective chlorination of 3-substituted oxindoles with *N*-chlorosuccinimide using calcium VAPOL as catalyst.^{17b} Based on this previous work, a calcium VAPOL-catalyzed one-pot double asymmetric cascade reaction was realized to provide chiral chlorinated oxindoles and geminal diamines simultaneously, which afforded two structurally complex and diverse chiral products with high levels of stereocontrol.^{17c}

We initiated this study of catalytic enantioselective amination of 3-phenyl-2-benzofuranone **1a** with dibenzyl azodicarboxylate **2** as the amination reagent. First, we screened CPAs as catalysts for the amination. The reaction smoothly afforded product **3a** in good yield at ambient temperature. When we used the vaulted biaryl (S)-VAPOL **P1** and (S)-VANOL **P2** phosphoric acids as catalysts, we found that the enantioselectivities were poor (Table 1, entries 1 and 2). Utilization of (R)-TRIP **P3**, a typically successful BINOL based catalyst, resulted in no improvement in the enantioselectivity (Table 1, entry 3). We were pleased to see that there was an appreciable increase in the enantioinduction when using 9-anthracenyl CPA **P4** (Table 1, entry 4). Varying the alkyl group on the diazo compound had no improvement in the selectivity. The best results were obtained with the benzyl substituted diazo compound. Lowering the temperature had no effect on the enantioselectivity. Next we screened chiral calcium phosphate as the catalyst. The calcium salt of 9-anthryl CPA **P5** exhibited very poor enantioselectivity in comparison to its acid (Table 1, entry 5). We speculated that varying the type of sterically hindering groups could find meaningful results. When using a 4-*tert*-butyl-phenyl substituted calcium phosphate **P6** to catalyze the reaction, we observed good enantioselectivity (Table 1, entry 6). When we replaced the (R)-BINOL backbone with the (R)-[H₈]-BINOL skeleton, we found significant improvement (Table 1, entry 7). The enantioselectivity of the reaction was indeed improved to 79%. In the next stage, 4-*tert*-butyl-phenyl substituted (R)-[H₈]-BINOL calcium phosphate **P7** was used to catalyze the amination of **1a**. Further attempts to improve the enantioselectivities by changing to alternative solvents such as chlorobenzene, trifluoromethylbenzene, dichloromethane, ether, tetrahydrofuran, and 1,4-dioxane were carried out (Table 1, entries 8–13), and the results indicated that solvent effect played an important role in enantioselectivities, with trifluoromethylbenzene being superior. Further optimization found that a low catalyst loading (1 mol %) could still provide high yield and enantioselectivity in the reaction (Table 1, entry 14).

Having established the optimized reaction conditions, we next explored the substrate scope of the reaction. We were pleased to find that consistently excellent enantioselectivities were achieved, and the results are summarized in Scheme 1. As illustrated, a wide range of 3-aryl-2-benzofuranones smoothly

Table 1. Condition Optimization for Amination of 3-Phenyl-2-benzofuranone **1a with Dibenzyl Azodicarboxylate **2**^a**

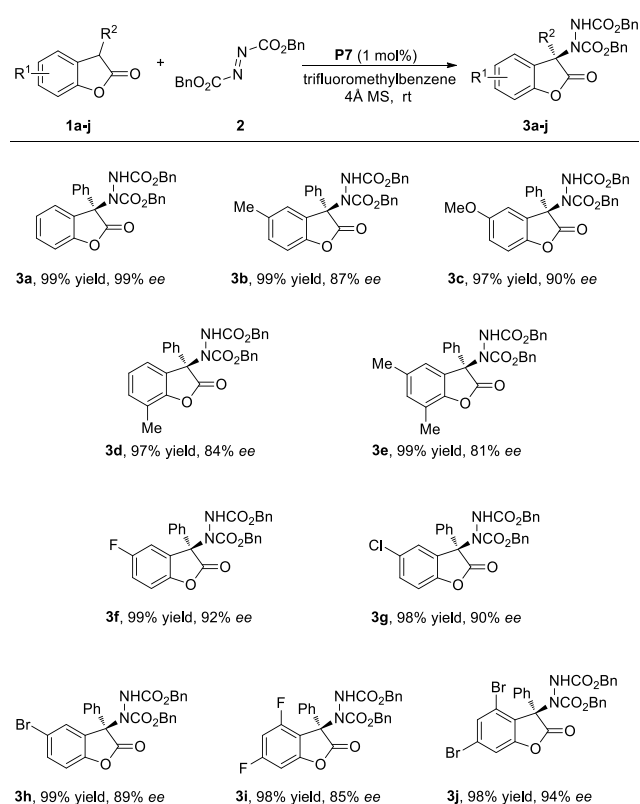


entry	catalyst	solvent	time (min)	ee (%) ^b	yield (%) ^c
1 ^d	P1	toluene	10	10	92
2	P2	toluene	10	6	96
3	P3	toluene	10	3	93
4	P4	toluene	10	80	92
5 ^e	P5	toluene	30	0	96
6	P6	toluene	30	56	92
7	P7	toluene	30	79	93
8	P7	Cl–Ph	30	96	95
9	P7	CF ₃ –Ph	30	99	99
10	P7	CH ₂ Cl ₂	30	90	96
11	P7	ether	30	50	99
12	P7	THF	30	16	90
13	P7	1,4-dioxane	30	10	87
14 ^f	P7	CF ₃ –Ph	30	99	99

^aReaction conditions: **1a** (0.025 mmol), **2** (0.03 mmol), catalyst, solvent (1.1 mL), and 4 Å MS (25 mg) were stirred under argon at room temperature. ^bEstablished by HPLC. ^cIsolated yield. ^dEntries 1–4: 10 mol % catalyst was used. ^eEntries 5–13: 5 mol % catalyst was used. ^fEntry 14: 1 mol % catalyst was used.

underwent the amination to give the products in excellent yields. The presence of electron-donating groups on the 2-benzofuranone core have little effect on the yield and enantioselectivity (*ee* was up to 90%) (**3b–3e**). Similarly mono-/disubstituted electron-withdrawing groups like fluoro, chloro, and bromo on the 2-benzofuranone gave comparable results (**3f–3j**) to the electron-donating groups.

The effects of substituents on the phenyl group at the α -position were next investigated. Initially, we tested electron-donating groups like methyl and methoxy on the phenyl group and found the enantioselectivities improved further compared to electron-donating substituents on 2-benzofuranone (**3k–3m**). Introduction of electron-withdrawing groups (**3n–3q**) on the phenyl group at the α -position greatly enhanced the

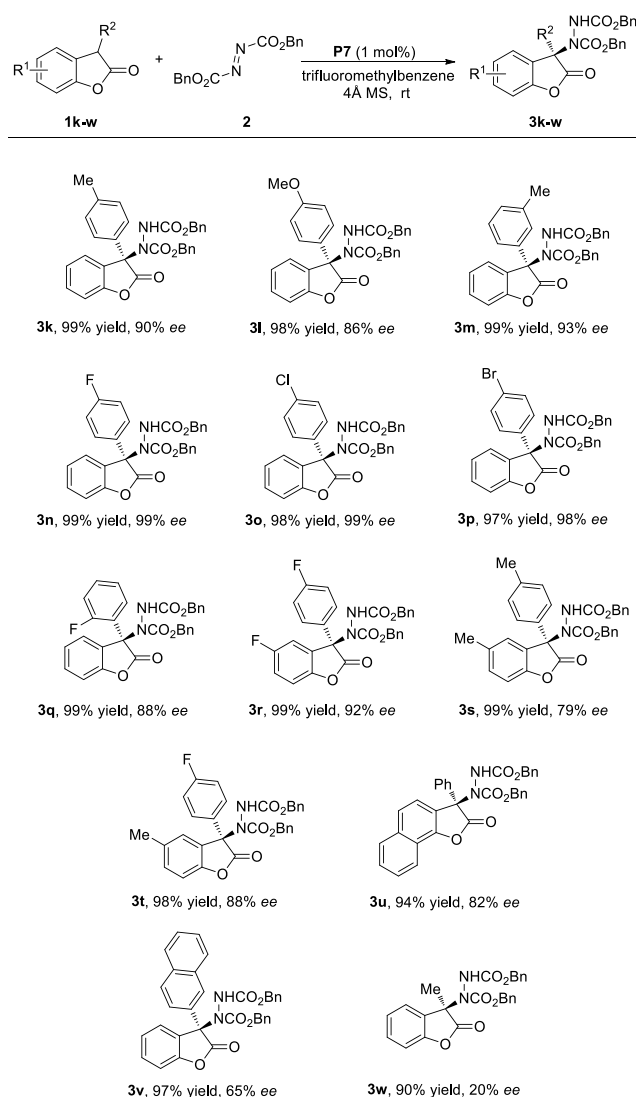
Scheme 1. Substrate Scope of Group on the 2-Benzofuranone Core^{a,b,c}

^aThe reaction condition: **1a-j** (0.025 mmol), **2** (0.03 mmol), and **P7** (0.3 mg, 1 mol %) were stirred in trifluoromethylbenzene (1.1 mL) with 4 Å MS (25 mg) as an additive under argon gas for 30 min. ^bIsolated yields. ^cDetermined by HPLC.

enantioselectivity (*ee* was up to 99%) in comparison to other substituents on the 2-benzofuranone.

However, an *ortho* fluoro substituent on the phenyl group at the α -position decreased the enantioselectivity (88% *ee*) in comparison to the *para* fluoro substituted counterpart (**3q** vs **3n**). We explored the use of two electron-withdrawing or electron-donating groups, among which the difluoro substitution being a good substrate (92% *ee*, **3r**), but two electron-donating groups (methyls) had a adverse impact on the enantioselectivity (79% *ee*, **3s**). Introducing both fluoro and methyl groups had no adverse effect on the enantioselectivity (88% *ee*, **3t**). We were pleased to find that the reaction also works for 3-phenylnaphthofuranone (**3u**), giving the product in high yield, albeit with lower enantioselectivity in comparison to the 3-phenylbenzofuranone (**3u** vs **3a**). Substrate introducing a β -naphthyl ring versus a phenyl at the α -position had an adverse effect on the enantioselectivity (65% *ee*) and showed that only the smaller phenyl ring at the α -position (**3v**) can be tolerated in our method.

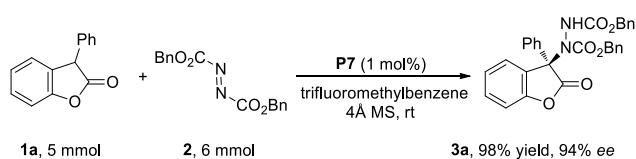
To further probe the limits of the reaction we used 3-methyl-2-benzofuranone as a substrate for the amination with the conditions in Scheme 2. Unfortunately, though we found a 90% conversion, the product was only obtained with a 20% *ee* (**3w**). The presence of the phenyl group at the α -carbon is a necessary requirement for this method's overall success. We also tried the reaction in the large-scale treatment of **1a** (1.05 g, 5 mmol) and **2** (1.78 g, 6 mmol) under optimized

Scheme 2. Substrate Scope of 3-Aryl-2-benzofuranones^{a,b,c}

^aReaction conditions: **1k-w** (0.025 mmol), **2** (0.03 mmol), and **P7** (0.3 mg, 1 mol %) were stirred in trifluoromethylbenzene (1.1 mL) with 4 Å MS (25 mg) as an additive under argon gas for 30 min. ^bIsolated yields. ^cDetermined by HPLC.

conditions, which gave the product **3a** in 98% yield and 94% enantioselectivity (Scheme 3).

Scheme 3. Gram-Scale Reaction



The absolute configuration of the product **3a** was determined to be (*R*), by comparison of the optical rotation with known compounds in reported literature.^{11b} Although a detailed mechanism is not yet established, our previous studies employing chiral calcium phosphates as catalyst gave us insight into a possible reaction mechanism.¹⁷ As shown in Figure 2, we believed the chiral calcium phosphate complex binds to

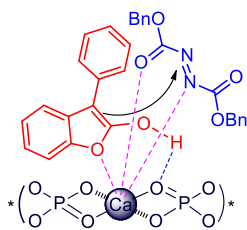


Figure 2. Proposed transition state for enantioselective amination.

activate both the substrates and force them in closer proximity. The Lewis basic phosphoryl oxygen activates the 2-benzofuranone by H-bonding interaction with its enol tautomer. These interactions provide an enantioselective sphere and promote the formation of highly enantioselective products.

In conclusion, we successfully developed a 4-*tert*-butyl phenyl substituted (*R*)-[H₈]-BINOL calcium phosphate catalyzed enantioselective amination of 3-aryl-2-benzofuranones **1** with dibenzylazo dicarboxylate **2**. The reaction has broad substrate scope, requires short reaction times, and requires a relatively low catalyst loading (1 mol %). The products are obtained in high yield and excellent enantioselectivity with mild conditions at room temperature. The coordination of nitrogen at the α -position of the 3-aryl-2-benzofuranones gives products, which could be potentially transformed into natural products/precursors and medicinally important compounds. The use of a nontoxic and environmentally friendly alkaline earth metal ion (calcium) salt offers a green approach and is an alternative to use of potentially toxic metal ions.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c03059>.

General condition, experimental procedures, characterization, copies of NMR spectra and HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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