Asymmetric Synthesis

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Enantioselective Base-Free Electrophilic Amination of Benzofuran-2(*3H*)-ones: Catalysis by Binol-Derived *P*-Spiro Quaternary Phosphonium Salts**

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Benzofuran-2(3*H*)-ones are important building blocks that are found in a large variety of natural products,[1] potential medicines,[2] and other highly functionalized compounds.[3] Many of them feature a chiral quaternary stereocenter at the C3 position of the heterocyclic ring (Figure 1).[1c–f]

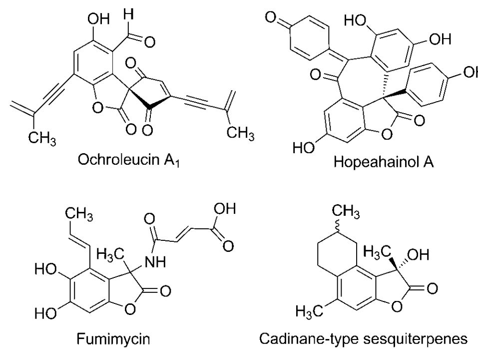

Figure 1. Examples of chiral benzofuran-2(3*H*)-ones.

However, enantioselective synthesis of such significant chiral benzofuran-2(3*H*)-ones remains a considerable challenge. Catalytic enantioselective introduction of substituents at the C3 position represents the most direct approach to chiral benzofuranones. For instance, Vedejs et al. and Hill and Fu have presented the asymmetric Black rearrangement of O-acylated benzofuranones by means of chiral derivatives of 4-dimethylaminopyridine (DMAP) to afford enantioenriched C-acylated isomers with up to 98% enantiomeric excess.[4,5] Very recently, two other groups reported the enantioselective conjugate addition reactions of benzofuran-2(3*H*)-ones to α,β-unsaturated carbonyl compounds, in which chiral thioureas and amines were used as catalysts.[6] Enantioselective introduction of a heteroatom group at the C3 position would substantially broaden the benzofuranone chemistry and offer more functionalized chiral products. Herein, we present a hitherto unknown catalytic enantioselective amination of benzofuranones by employing a new class of rigid chiral *P*-spiro quaternary phosphonium salts as organocatalysts.

Over the past decades, organocatalysis that exploits the use of chiral quaternary ammonium salts has emerged as an area of intense interest in asymmetric synthesis owing to its operational simplicity and mild reaction conditions.[7,8] A number of quaternary ammonium salt catalysts have demonstrated useful levels of enantioselectivity in a wide range of asymmetric reactions. Furthermore, a recent breakthrough in this field involved the design and application of chiral quaternary phosphonium salts in catalytic asymmetric synthesis.[9] For examples, the group of Ooi developed a series of *P*-spiro tetraaminophosphonium salts as chiral Brønsted acids for substrate recognition and functional-group activation through hydrogen bonding.[9e–j] Maruoka and co-workers reported other chiral quaternary tetraalkylphosphonium salts and their use in asymmetric phase-transfer catalysis.[9m–o] Despite the above mentioned progress, this field is still in its infancy and the construction of new phosphonium catalysts is still in great demand to meet the need of many challenging asymmetric reactions.

Since 1,1′-binaphthyl-based enantiopure chiral materials are among the most readily available privileged sources of chirality, chemical modification of binaphthyls resulting in the formation of new modular structures for catalytic application has been a proven strategy for the development of novel chiral catalysts. We envisioned that the introduction of two chiral 2,2′-bis(methylene)-1,1′-binaphthyl moieties onto a phosphorus center would form a rigid *P*-spiro tetraalkylphosphonium framework, thus enabling a high level of asymmetric induction. A series of novel homochiral tetraalkylphosphonium bromides **1** possessing a [7.7] spirocyclic core were readily prepared by the reaction of (*S*)-4,5-dihydro-3*H*-dinaphtho[2,1-*c*:1′,2′-*e*]phosphepine[10] with (*S*)-3,3′-disubstituted 2,2′-bis(bromomethyl)-1,1′-binaphthyls and purified in analytically pure form after one simple recrystallization. Crystals suitable for X-ray diffraction analysis were obtained for the quaternary phosphonium salt **1a**.[11] The ORTEP view of this structure is shown in Figure 2. As expected, the two binaphthylmethylene units are twisted at the phosphorus center. The dihedral angle between the planes of the two naphthyl units is 69.1°. It was expected that the conformational rigidity imposed by the *P*-spiro scaffold could poten-

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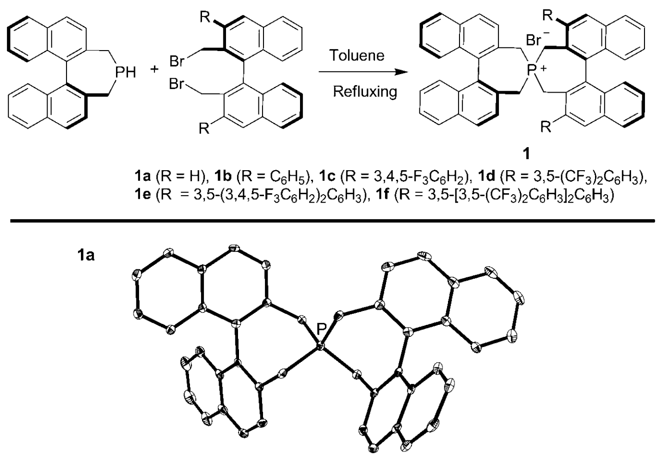


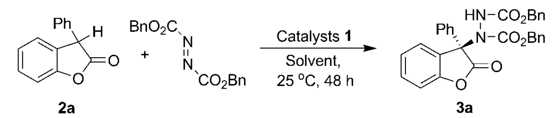
Figure 2. Synthesis of new quaternary phosphonium salts **1**. An ORTEP view (ellipsoids shown at 50% probability) of **1a** is provided (counter anion, calculated hydrogen atoms, and solvent molecules are omitted for clarity).

tially translate into a positive attribute in achieving a high level of asymmetric induction in the catalyzed reaction.

With these novel quaternary phosphonium catalysts in hand, we set out to examine their activity in the reaction of 3-phenylbenzofuran-2(3*H*)-one (**2a**) and (*E*)-dibenzyl diazene-1,2-dicarboxylate to identify the best catalyst and the optimal reaction conditions (Table 1). Gratifyingly, in the absence of any base, the simplest catalyst, **1a**, catalyzed this amination reaction in toluene at room temperature for 48 hours to give product **3a** in 39% yield with a 66% *ee* (entry 1). We were pleased to find that the introduction of bulky substituents on the catalyst had a remarkably beneficial effect on both the reactivity and the stereoselectivity. Thus, the presence of substituted phenyl groups on the 3,3′-positions of only one of the binaphthyl units could improve the *ee* value to up to 95% (entries 2–4) and the addition of another tier of aryl rings could further improve the *ee* value to up to 98% (entries 5 and 6). Among them, catalyst **1e** gave excellent yield and the highest enantioselectivity. A comparison of the results obtained in different solvents showed that this asymmetric transformation is highly sensitive to the solvent used (entries 7–11). Polar solvents generally gave lower *ee* values and toluene was found to be the best solvent for this reaction. Decreasing the amount of catalyst to 1 mol% caused only a slight decrease in the yield and the *ee* value of the product (entry 12).

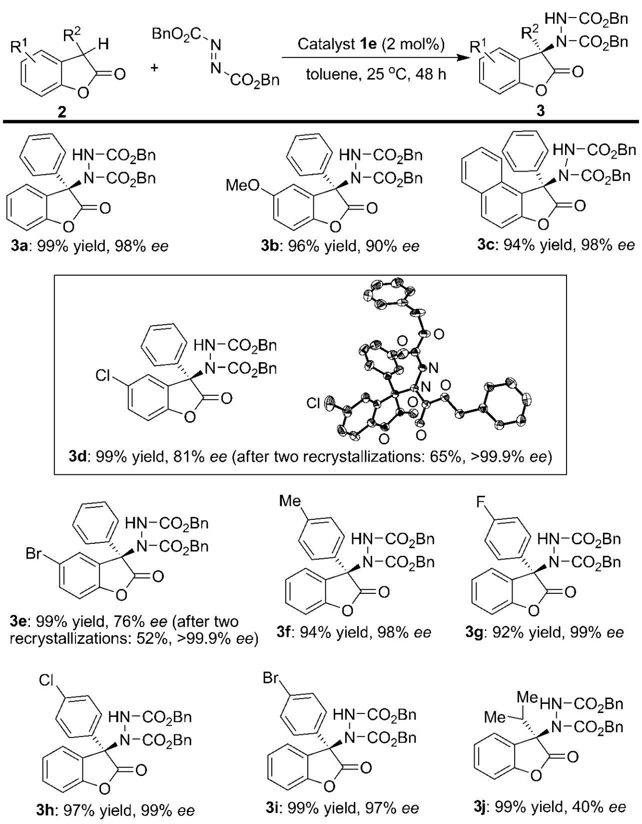
Under the optimized reaction conditions, the scope of this unprecedented enantioselective amination of benzofuranone was further examined in the presence of catalyst **1e** and the results are listed in Scheme 1. Substrates with electron-donating and electron-neutral groups on the benzofuranone gave the desired products in high yields and enantioselectivities (90–98% *ee*; **3a–c**). Halogen substitution at the 5-position of the benzofuranone had no impact on the activity of the amination, but a lower enantioselectivity was observed (**3d** and **3e**). The adduct **3d** was crystallized from CH_2Cl_2/petroleum ether, and its structure, including its absolute configuration, was determined by Röntgen diffraction studies.[11] 3-Arylbenzofuranones gave high yields and excellent enantioselectivities (**3f–i**). In addition, 3-isopropyl benzofur-

Table 1: Screening of novel quaternary phosphonium catalysts and optimization of reaction conditions.[a]



Entry	**1** (mol%)	Solvent	Yield [%][b]	*ee* [%][c]
1	**1a** (2)	toluene	39	66
2	**1b** (2)	toluene	85	65
3	**1c** (2)	toluene	80	95
4	**1d** (2)	toluene	80	90
5	**1e** (2)	toluene	99	98
6	**1f** (2)	toluene	87	95
7	**1e** (2)	CH_2Cl_2	38	65
8	**1e** (2)	Et_2O	99	90
9	**1e** (2)	THF	60	59
10	**1e** (2)	1,4-dioxane	65	27
11	**1e** (2)	CH_3CN	98	35
12	**1e** (1)	toluene	94	96

[a] See the Supporting Information for details concerning the reaction conditions. [b] Yields are of isolated pure products. [c] Determined by HPLC analysis using a chiral stationary phase. Bn = benzyl.



Scheme 1. Selected examples of catalytic enantioselective amination of 3-substituted benzofuran-2(3*H*)-ones. For the X-ray crystal structure the thermal ellipsoids are shown at 50% probability and the hydrogen atoms are omitted for clarity.

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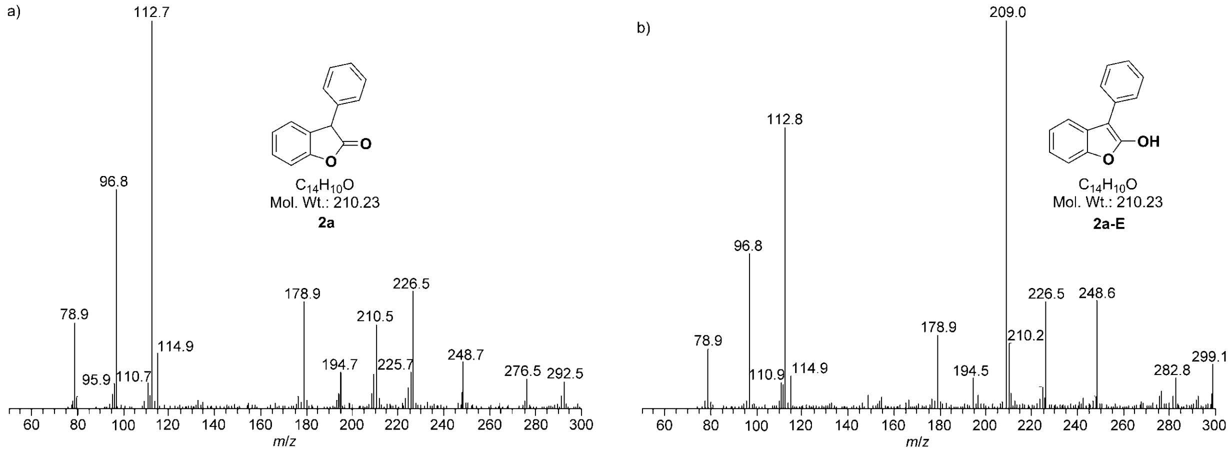

Figure 3. a) MS (ESI) spectrum of substrate **2a**. b) The new species detected by HPLC/MS (ESI) analysis of the reaction mixture of **2a** and dibenzyl diazene-1,2-dicarboxylate in the presence of catalyst **1e**.

anone also afforded the desired product **3j** in good yield but with only a moderate *ee* value.[12]

Mechanistically, the reactions that are conducted under homogeneous reaction conditions in the absence of any base are clearly distinct from phase-transfer catalysis. The lack of the possibility for the formation of hydrogen bonds as well as other interactions such as ionic attraction between the catalyst and the substrate present a rather intriguing case for mechanistic interpretation. While a pure sample substrate of **2a** was shown to be homogeneous by ^{1}H NMR analysis ([D$_8$]toluene) and its enol form undetectable on the timescale of the NMR experiment,[13] trace amounts of a new species were detected with the help of HPLC/MS methods during its reaction with dibenzyl diazene-1,2-dicarboxylate in the presence of catalyst **1e**. As shown in Figure 3, this new species exhibits a distinct mass spectrum (Figure 3b) when compared with that of **2a** (Figure 3a) and is characterized by a base peak at m/z 209.0. The structure of this species was assigned as **2a-E**, that is, the enol form of **2a**.[14] This observation led us to propose that the highly enantioselective electrophilic amination of **2a** stems from the efficient formation of the enol in a dynamic process whereby a strong π–π interaction between the enol form of **2a** and the axially chiral binaphthylene moiety of **1e** ensures a favorable reversal in the equilibration between the lactone and the enol (Figure 4), which is reminiscent of the induced fit in enzymatic reactions. DFT calculations[15] based on catalyst **1a** and lactone **2a** indicate that the formation of the catalyst–enol complex (**C·E**) is approximately 3.4 kcal mol^{-1} more favorable than that of the catalyst–lactone complex (**C·L**). With the help of the X-ray structure of **1a** and DFT structure optimization, we were able to qualitatively emulate the way the enol is bound to the catalyst through π–π interactions. Gratifyingly, the binding mode with the lowest energy was found to be one that leads to effective shielding of the *Si* face of the enol, thereby leaving its *Re* face open to the electrophilic attack by the azodicarboxylate. The enol form of **2a** is sandwiched between the catalyst and the azodicarboxylate. Crucial for the reactivity, is the catalytic electrophilic activation of the nitrogen donor reagent by the phosphonium group. Other stacking combinations on different faces of the catalyst that would move the azodicarboxylate away from the phosphonium are not reactive since the electrophilic activation of the azodicarboxylate is not permitted. Although the true mechanism of this reaction requires further detailed

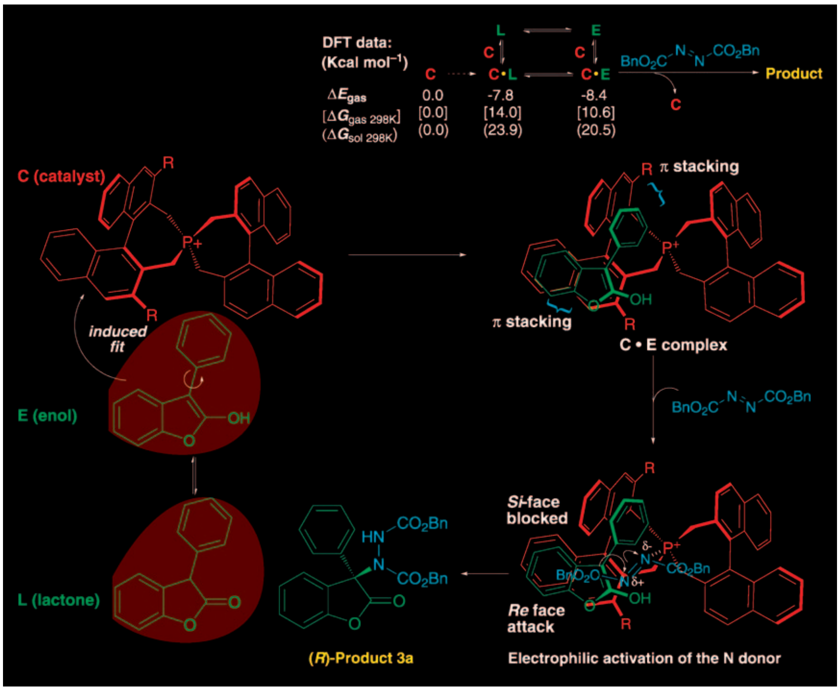

Figure 4. Proposed transition-state assembly for the catalytic enantioselective amination of 3-substituted benzofuran-2(3*H*)-one.

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studies, the working model proposed in Figure 4, which is distinctly different to the mechanism of conventional phase-transfer catalysis, explains both the high level of reactivity and the face selectivity of the asymmetric catalysis by the novel binaphthyl-based phosphonium salts.

In summary, a new class of rigid binol-derived *P*-spiro quaternary phosphonium salts were designed and synthesized. Their catalytic activity and stereoselectivity have been clearly demonstrated in the development of the first highly enantioselective amination of benzofuranones. These studies also offer valuable insights into the rational design of novel catalyst systems that have alternative mechanisms for asymmetric induction. Further investigation of the reaction mechanism, as well as the utility of these novel catalysts in other unexplored asymmetric transformations are ongoing and will be reported in due course.

Experimental Section

A mixture of substituted benzofuran-2(3*H*)-one (0.1 mmol), (*E*)-dibenzyl diazene-1,2-dicarboxylate (35.8 mg, 0.12 mmol), and (*S*,*S*)-**1e** (2.7 mg, 2 mol%) in toluene (2 mL) was stirred vigorously at 25 °C for the stated time. After the reaction was complete (determined by TLC), the resulting mixture was concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/petroleum ether = 1/10 as eluent) to afford the desired adduct **3**. The product was identified by NMR spectroscopy. The enantiomeric excess of the product was determined by HPLC using a chiral column.

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[11] CCDC 777504 (**1a**) and 795088 (**3d**) contain the supplementary crystallographic data. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

[12] The amination reaction of 3-isopropyl benzofuranone was carried out at 0 °C for 24 h.

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