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Biomimetic Approach to the Catalytic Enantioselective Synthesis of Flavonoids

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Supporting Information

ABSTRACT: Herein is reported the direct asymmetric addition of phenol nucleophiles to benzopyrylium salts as a means to produce enantioenriched flavonoid-like compounds. This enantioselective C−C bond construction was achieved through a chiral anion phase-transfer strategy that mimics the proposed biosynthesis of this structurally diverse set of natural products. The utility of this methodology was demonstrated in enantioselective synthesis of a 2,8-dioxabicyclo[3.3.1]nonane and a 2,4-diarylbenzopyran.

Flavonoid compounds containing 2,4-diarylbenzopyran or 2,8-dioxabicyclo[3.3.1]nonane skeletons comprise a large class of natural products with diverse activity (Figure 1A).[1,2] The proposed biosynthetic pathway proceeds through a benzopyrylium salt (**A**) that engages a phenolic compound (**B**) in either a simple addition reaction or a formal cycloaddition to form structures of the type **C** or **D**, respectively (Figure 1B).[2a,3] While progress has been made in the development of methods for the stereoselective construction of these skeletons, to date they have generally relied on the *de novo* formation of the pyran ring[4] and, therefore, have not provided access to the diversity enabled by a biomimetic route.

The development of an enantioselective biomimetic flavonoid synthesis requires a catalyst capable of promoting

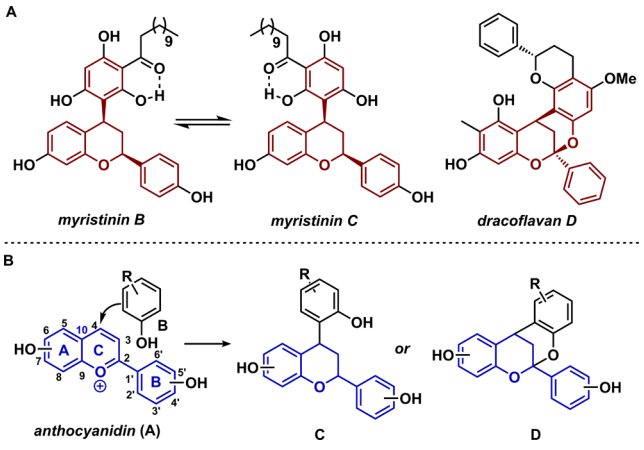

Figure 1. (A) Example of flavonoid natural products containing 2,4-diarylbenzopyrans or 2,8-dioxabicyclo[3.3.1]nonane subunit. (B) Proposed biosynthetic pathway.

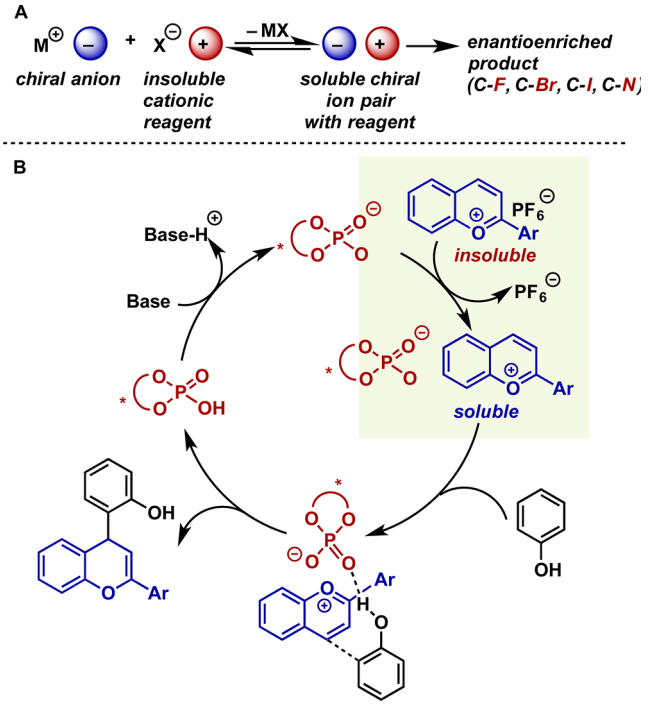

Figure 2. (A) General CAPT process. (B) Application of CAPT catalysis to benzopyrylium hexafluorophosphate.

stereoselective addition to a planar cationic electrophile. These species generally fall outside of the purview of typical Lewis and Brønsted acid catalysis. On the other hand, chiral anion phase-transfer (CAPT) catalysis has been used to engage a variety of cationic electrophiles as a means to construct asymmetric C−F, C−Br, C−I, and C−N bonds (Figure 2A).[5,6] Inspired by these works, we envisioned that this method might be used for the desired enantioselective C−C bond formation. In this scenario, CAPT of an insoluble benzopyrylium cation generates a soluble chiral benzopyrylium ion pair, which can react with phenols to generate enantioenriched flavonoid-type products and release the chiral phosphate (Figure 2B).

The reaction between 6-Br, 4′-MeO-benzopyrylium hexafluorophosphate (**1a**) and 1-naphthol was chosen as model reaction to investigate this hypothesis (Table 1).[7] In the presence of 2 equiv of Na_3PO_4 and 10 mol % of (*S*)-C_8-MES (**2a**), **1a** reacted smoothly with 1-naphthol in toluene to give

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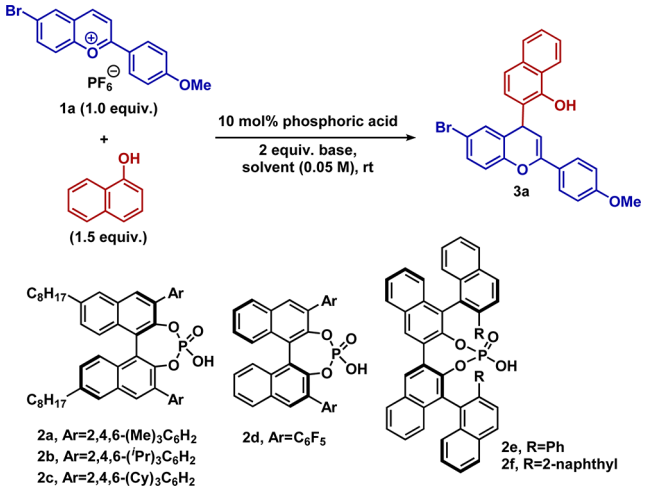
Table 1. Optimization of the Reaction Conditions[a,b]



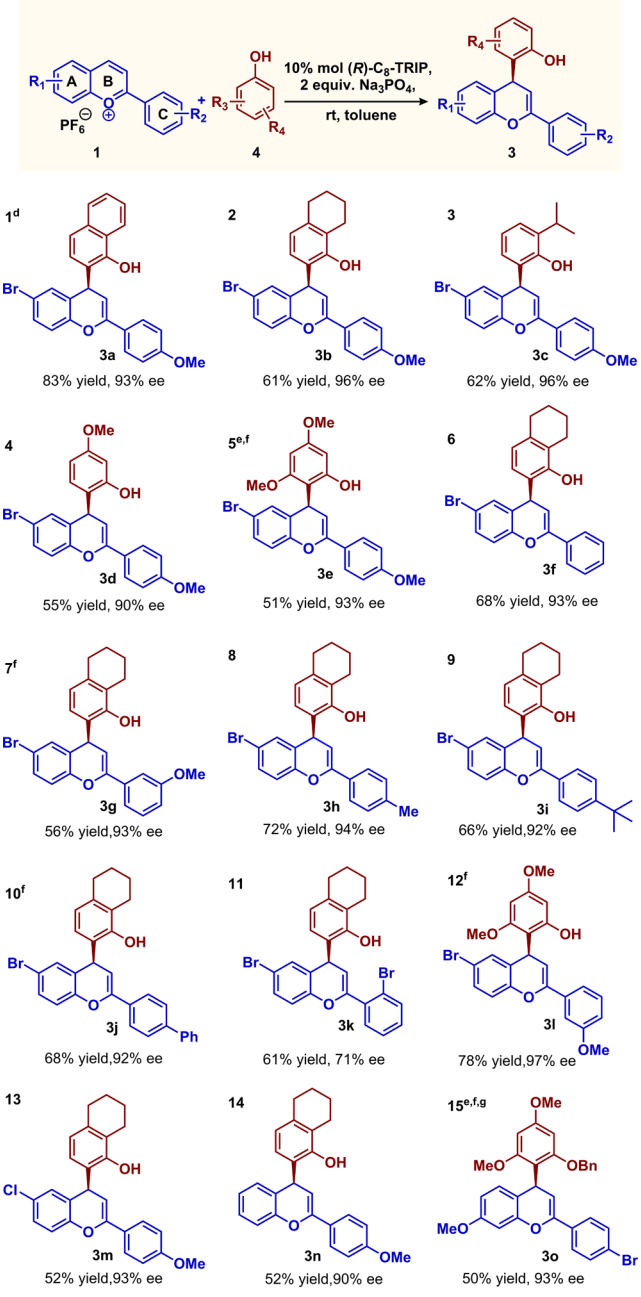
entry	cat.	solv	base	conv. (%)	ee (%)
1	**2a**	toluene	Na_3PO_4	>95	−28
2	**2b**	toluene	Na_3PO_4	>95	−61
3	**2c**	toluene	Na_3PO_4	>95	−61
4	**2d**	toluene	Na_3PO_4	>95	+14
5	**2e**	toluene	Na_3PO_4	>95	−51
6	**2f**	toluene	Na_3PO_4	>95	−48
7	**2b**	Et_2O	Na_3PO_4	–[c]	–[c]
8	**2b**	hexanes	Na_3PO_4	low	−12
9	**2b**	toluene/hexanes (1:1)	Na_3PO_4	>95	−38
10	**2b**	toluene	$NaHCO_3$	>95	−60
11	**2b**	toluene	K_2CO_3	>95	−18
12	**2b**	toluene	Na_2CO_3	>95	−60
13[d]	**2b**	toluene	Na_3PO_4	>95	−83
14[d]	**2b**	toluene	$NaHCO_3$	low	−85
15	none	toluene	Na_3PO_4	>95	–
16[d,e]	**2b**	toluene	Na_3PO_4	>95 (57)[g]	−93
17[d–f]	**2b**	toluene	Na_3PO_4	>95 (83)[g]	−93

[a]Conversion determined by NMR spectroscopy. [b]ee determined by chiral HPLC analysis of the crude reaction mixture after filtration through a short plug of silica gel. [c]Reaction was complex; therefore, the conversion and ee were not determined. [d]Reaction performed under N_2. [e]Reaction performed at 0 °C. [f]10 mg 4 Å molecular sieves was added. [g]Yield of isolated product.

the desired product (**3a**) with good conversion and low enantioselectivity (−28% ee; Table 1, entry 1). Investigation of other catalysts revealed that chiral phosphoric acids (*R*)-C_8-TRIP (**2b**) and (*R*)-C_8-TCYP (**2c**) provided the highest levels of selectivity (61% ee, Table 1, entries 2 and 3). Variation in the reaction solvents or the stoichiometric bases did not improve the enantioselectivity of **3a** using (*R*)-C_8-TRIP (**2b**) as the catalyst (Table 1, entries 7−12). We hypothesized that the product might be sensitive to oxygen (air).[8,9] Accordingly, performing the reaction under nitrogen resulted in an improvement in the enantioselectivity to 83% ee (Table 1, entry 13). Furthermore, we found that the reaction reached full conversion even if in the absence of the catalyst (Table 1, entry 15). Finally, lowering the reaction temperature to 0 °C and adding 4 Å molecular sieves furnished **3a** in 83% yield and 93% ee (Table 1, entry 17).

The scope of the chiral anion-catalyzed C−C bond forming reaction was explored using the optimized conditions; however, changing from 1-naphthol to less nucleophilic phenols resulted in lower conversion. Increasing the temperature from 0 °C to room temperature improved conversion, allowing neutral and electron-rich phenols to afford the corresponding products in good yields and excellent enantioselectivities (Table 2, **3a**−**3e**).

Table 2. Substrate Scope[a–c]



[a]Unless otherwise noted, all reactions were carried out with **1** (0.05 mmol), phenol **4** (0.075 mmol), phosphoric acid catalyst (0.005 mmol), 10 mg 4 Å molecular sieves, and Na_3PO_4 (0.1 mmol) in toluene (1.0 mL) for 2−12 h under N_2 at rt. [b]Isolated yields after chromatography. [c]ee was determined by chiral HPLC analysis. Absolute stereochemistry of **3f** assigned by X-ray analysis of the 2,8-dioxabicyclo[3.3.1]nonane derivative (see SI). Remaining stereochemistries assigned by analogy. [d]Reaction performed at 0 °C. [e]Ethyl acetate was used as solvent. [f](*R*)-C_8-TCYP (**2c**, 0.005 mmol) used as catalyst. [g]ee was determined after conversion of the phenol product (unstable under air) to corresponding benzyl ether, 50% over two steps.

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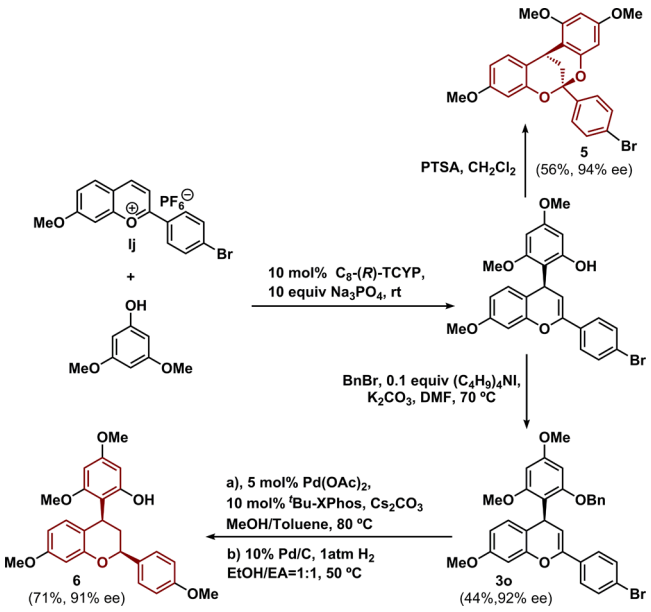
Scheme 1. Synthesis of 2,8-Dioxabicyclo[3.3.1]nonane Subunit Skeleton and 2,4-Diarylbenzopyrans



Substrates in which the C-ring of the benzopyrylium salt was substituted with an electron-rich group at the *para* or *meta* position furnished the corresponding product in excellent enantioselectivities (Table 2, **3g**−**3j**, **3l**). On the other hand, substitution at the *ortho*-positions of C-ring decreased the enantioselectivity, although good yield was maintained (Table 2, **3k**). With respect to the substitution at A-ring of benzopyrylium salt, substrates bearing electron-poor and electron-rich groups delivered the corresponding product in moderate yields with excellent enantioselectivities (Table 2, **3m**−**3o**).

On the basis that many flavonoid natural products possess 7-hydroxy and 4′-hydroxysubstituents, we sought to extend the method to a 7 and 4′-substituted benzopyrylium hexafluorophosphate salt. After many attempts, 7-MeO, 4′-Br-benzopyrylium hexafluorophosphate (**1j**) was identified as optimal for this substitution pattern. For example, **3o** was formed in 50% yield and 93% ee.[9] Moreover, chiral anion-catalyzed reaction of benzopyrylium salt **1j** with 3,5-dimethoxyphenol was followed by acid-catalyzed cyclization to furnish 2,8-dioxabicyclo[3.3.1]nonane **5** in 56% yield and 94% ee (Scheme 1). This skeleton is found in a variety of natural products that demonstrate a wide range of biological activity.[10] Derivatization of the enantioenriched product in Table 1 was also investigated. Reaction **1j** with **2** (on a 1.0 mmol scale) furnished compound **3o** in 44% yield and 92% ee (no loss of ee).[11] Palladium-catalyzed conversion of the bromosubstituent of **3o** to a methoxy group,[12] followed by reducing with H_2 produced phenol **6** without loss of enantiomeric purity (71% in 2 steps, 91% ee).[13] Notably, phenol **6** contains the core of myristinin **B** and **C** (Figure 1A).

In conclusion, the first example of CAPT catalysis for the enantioselective delivery of carbon-based electrophiles is reported. The use of benzopyrylium-type cations as electrophiles for phenols mimics the pathway proposed for the biosynthesis of flavonoid natural products and, therefore, allows for an expedient enantioselective entry into this class of compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b05939.

Crystallographic data (CIF)

Experimental procedures, and compound characterization data. (PDF)

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Notes

The authors declare no competing financial interest.

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(8) Higher ee was also observed when the reactions in Table 1 were reinvestigated under a N_2 atmosphere (see Table S1). The product was unstable in the air to some extent. The lower ee obtained under air atmosphere might result for catalyst inhibition by the oxidation side-product sequesters resulting in increased product formation from uncatalyzed background reaction (See Table 1, entry 15). Meanwhile, <2% ee was observed when racemic product (**3a**) was subjected to the standard reaction under air atmosphere, suggesting that the selectivity does not result from an oxidative kinetic resolution.

(9) See Supporting Information for details.

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(13) The relative configuration was determined by NOE (see Supporting Information).

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